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JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

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The *Journal of Clinical and Experimental Psychopathology* was founded in 1939 by V. C. Branham, M.D., as the *Journal of Criminal Psychopathology*. In 1944 the title was changed to the *Journal of Clinical Psychopathology*; in 1951 the journal became the *Journal of Clinical and Experimental Psychopathology*. The present title (*Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology*) was assumed in 1954.

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Symposium on New Perspectives in Neuroendocrinology

Clinical Psychopathologic Conferences are included as a regular feature of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY. This section will attempt to further the elucidation of correlations and associations between clinical, neurologic, psychologic, and biologic elements. Subsequent issues will present clinical case presentations illustrative of psychophysiopathologic disorders. These will be contributed by psychiatric hospitals, clinics, and psychiatrists throughout the world. Manuscripts together with accompanying illustrations should be forwarded to the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY, 30 East 60th Street, New York, N. Y., Attention: Editor, Clinical Psychopathologic Conferences.

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

Incorporating the International Record of Psychiatry and Neurology

PSYCHIATRY ABSTRACTS

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY
&
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SYMPOSIUM ON NEW PERSPECTIVES IN NEUROENDOCRINOLOGY

On Neuroendocrinologic Research in Psychiatry During the Kraepelin-Freud Centennial Year

The current issue of the JOURNAL OF CLINICAL & EXPERIMENTAL PSYCHOPATHOLOGY is devoted in its entirety to endocrinologic aspects of clinical and research psychiatry.

Together with the symposium on chlorpromazine and the reports on reserpine (which were presented in earlier issues of this year) and with the recently held American Psychiatric Association round-table discussion on "Psychobiology 1956" (which will be presented in the final number of this year), the current volume presents a perspective of a new vitality in psychiatric development. It is a panorama, for the first time, of multiple approaches to the therapeutic problem of the psychoses in general and schizophrenia in particular. Though new, the therapies have definite historical and biologic links to the past contributions by Cerletti, Hoskins, Meduna, Moniz, and Sakel,[1] which comprised until recently the only physiodynamic methods available to clinical psychiatrists. It is a perspective that finally has turned from the past and the blinding emphasis on psychodynamics to a searching study of physical phenomena and their relation to psychologic manifestations.

This perspective encompasses not only the influence of physiologic forces on psychologic characteristics even to the development of personality itself, but also the consequence of psychologic experience (environmental forces) upon physiologic phenomena. It is a per-

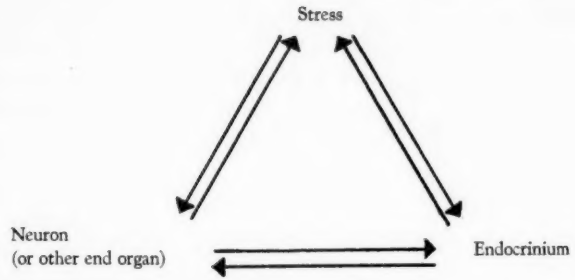
spective that holds promise that the works of Kraepelin[2, 3] and Freud will be brought closer together and with it a better understanding of the psychologic resultant of physiologic phenomena and the biologic effects of psychologic forces.

Paradoxically, this centennial year of Freud's birth, whose main contribution was in the field of psychodynamics, has been marked by the acceptance of the newer physiodynamic agents as the organic therapies of choice in the treatment of the psychoses and by the development of a widespread research effort to determine their method of action as well as the etiologic and pathogenetic mechanisms underlying the psychiatric disorders. This is a fitting coincidental memorial to both Freud and Kraepelin. As early as 1950 van Ophuijsen, in his introduction to the "Endocrinologic Orientation to Psychiatric Disorders,"[2] recalled Freud's remark to him in 1927: "Of course, you know, I am firmly convinced that one day all these disturbances we are trying to understand will be treated by means of hormones or similar substances." Sandor Rado has presented a direct translation of Freud's statements in this vein as follows: "We must bear in mind that some day all our provisional formulations in psychology (*psychologische Vorlaufigkeiten*) will have to be based on an organic foundation. It will then probably be seen that it is special chemical substances and processes which achieve the effects of sexuality and the perpetuation of individual life in the life of the species."[2] And William James also has said that psychology cannot be fully explained just by psychology.

The studies reported here continue the pioneer efforts to link the endocrinium and the nervous system in a neuroendocrine framework to psychiatric disturbances. They are in areas that have not as yet attained acceptance, perhaps because of the discrepancies so often noted in their findings.

However, discrepancies in findings should not be unexpected, since many of the problems of standardization of research in this field have yet to be solved. Difficulties that are generally present in research are particularly acute in experimental and clinical psychiatry, for there is great difficulty in establishing similar points of reference to patient populations by diagnosis, age group, and years of illness; to laboratory procedures applied; to the point in time that the particular hormonal disequilibriums are studied;[4] to the concentration of any physiodynamic substance in its absolute, relative, and operative expression;[4] to the elucidation of "the existence within the organism of one or several counter-factors (antidynes) . . . which can reverse the direction of the body function or reaction," both to endogenous forces and to therapeutic substances;[4] and to the recognition of the individual patient's ability to mobilize physiologic defense mechanisms that may alter the influence of any biochemical or pharmacologic agent.

But, it is a reality and a fact accepted by all workers in the biologic aspects of psychiatry that: "The organism functions in relation to an external and an internal environment. At all times, the internal environment is integrating within itself elements from the external environment, even as it exerts its own influence upon the external environment. In the



biochemistry of the body and in the personality and mental status of the individual, we find the ultimate results of the interaction between the two."[4]

The neuroendocrine system is the mediating mechanism through which environmental stresses exert their effects; the neuron is the end organ upon which they act in the psychoses and psychoneuroses, while the cardiovascular, gastrointestinal, and respiratory systems are the target organs in psychosomatic disorders.

Studies directed to uncovering the relationship between physical phenomena and psychologic manifestation, whether normal or aberrant, are essential to the further development of this new perspective and will be encouraged by all who are devoted to the cause of psychiatric science.

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Some Recent Developments in Psychoendocrinology*†

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There are many signs of an intimate relationship between endocrine glands, as parts of the whole psychosomatic organization, and mental disorder, but so far, evidence of any etiological relationship has been indefinite. Henderson and Gillespie point out that we know that mental disease commonly breaks out at puberty, pregnancy, or the menopause, that the thought content of a psychosis may often be sexually colored, and that disturbance of the sexual functions and paresthesias are common symptoms. Menstruation with tension and other neurotic symptoms has been much discussed. It is known that relief of the neurotic tension symptoms can be assisted by endocrine means with progesterone, even if psychologic factors also need attention, as work by Greene et al has shown. However, several factors showed that it might be worth while to re-examine this relationship that we know must exist between the nervous and endocrine systems, and to see if unifying concepts can be worked out, even if so far we have been unable to understand the detail of the mechanisms involved.

Improvement in some endocrinological laboratory methods has widened considerably the scope of investigations and of diagnostic possibilities. I^{131} tracer methods now play an important part in the investigation of the thyroid function, and the uptake of the isotope has been seen to vary in relation to changes in the mental state. It has also become evident that the basal metabolic rate, while usually in agreement with the results of I^{131} tracer investigation, is not always so, and where it is not so, a state of peripheral undersensitivity to thyroid hormone can be detected. This was already suggested by Hoskins and Sleeper when they found schizophrenic patients who were insensitive to enormous amounts of thyroid preparations. The I^{131} tracer method also permits us to differentiate between primary or secondary (pituitary) disturbances.

Similarly, our knowledge of adrenal and gonadal function has been widened by the use of methods for the determination of 17-ketosteroids and corticoids and of chromatographic fractionation of the various ketosteroids. Methods for the determination of the various pituitary anterior lobe hormones are still in their infancy, certainly not yet ready for routine

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* Based on a paper read at the Quarterly Meeting of the Royal Medico-Psychological Association, London, Nov. 9, 1955.

† This paper and those by Reiss (p. 431) and Robinson et al (p. 439) are also being published in the July, 1956, INTERNATIONAL RECORD OF MEDICINE & GENERAL PRACTICE CLINICS.

clinical use, but some are already suitable for use in research cases. When the functions of both the thyroid and the adrenal are disturbed, as indicated by the combined results of the tracer and steroid estimations, and when there is a clinically recognizable deviation in body growth or gonads, then it is probable that a disturbed pituitary anterior lobe function exists. A further factor has been that the production of more reliable hormone preparations is progressing.

Last, but perhaps most important, is the fact that the conception of the possible role of endocrines in relation to psychiatry has changed. The original approach to the problem of endocrinological psychiatry was a rather unfortunate one, since the function of certain glands was too much connected with specific psychologic functions. These functions were related too readily to animal experiments. One may cite the loss of fighting spirit of the cock after removal of the testicles and its return after reimplantation of the testicles. We know now that it is by no means always the sex hormone that has a relation to the "fighting spirit," but that the "fighting spirit" depends on a much greater multitude of endocrine and psychologic and genetic factors. We know now that the same hormone can have quite different psychologic action if given to different individuals with varying personality patterns.

Progress has been delayed because we have ignored the common association of mental illness with phases of intense endocrine change at puberty, pregnancy, and the menopause and have continued too long to look for direct causal relationships, in spite of the established fact that diseases of the endocrine glands are not significantly correlated with mental illness, or vice versa. No particular neurosis or psychosis has yet been directly etiologically linked with a particular endocrine disorder. A state of thyroid hyper- or hypofunction is not consistently associated with psychiatric illness, nor are clinically recognizable disorders of the adrenals or gonads or pituitary, though at times all are associated with mental breakdown. We have rather taken the view that, as in puberty, pregnancy, and the menopause, it is the variation in endocrine function that is important, but that, as in these crucial epochs, it is not merely the occurrence of endocrine variation that is significant, but the degree to which that variation differs from a particular individual's normal range, together with the stability of the personality in which these changes occur. Furthermore, it is the personality pattern that will determine the form of the subsequent psychiatric disorder, no matter what the type of endocrine deviation may be. In fact, it is not only the type of hormone that is important, but alteration in its quantity, in so far as this is related to the whole hormone equilibrium.

The number of hormones known to influence the development and function of the nervous system is increasing. Hypothyroidism has been recognized for years as producing arrest of intellectual maturation in the young and as being linked with anxiety in many adults. Cortisone, ACTH, and dehydroisoandrosterone (diandrone) can in certain persons precipitate a psychosis or severe behavior disorder. Conversely, clinical improvement has been reported by Strauss et al in some very immature and socially inadequate schizophrenics and by Sands and Chamberlain in adolescent cases of inadequate personality. Estrogens diminish the quantity of the sexual activity in the male and, in so far as psychoses are concerned, can make an existing psychosis temporarily more acute in certain cases. A similar

TABLE I
Thyroid Activity
(Age Group 18 to 21 Years)

	Total no. investigated	No. in normal range	No. below normal range	Per cent below normal range	No. above normal range	Per cent above normal range
Royal Army Medical Corps	78	68	4*	5.1	6†	7.7
Psychiatric patients	131	97	18‡	13.7	16§	12.2

* Lowest 24 hour uptake 20 per cent.
† Highest I_t 12.4.
‡ Lowest 24 hour uptake 4.2 per cent.
§ Highest I_t 18.3.

effect was obtained in some patients treated by chorionic gonadotrophin (Pregnyl). In fact, the whole question of the activation of psychiatric disorders by hormones, including the well recognized activation by insulin, needs further investigation. Obviously hormones can influence the function of the nervous system. The problem is to determine the cases likely to be benefited rather than the reverse.

Robinson assessed the thyroid activity of 110 newly admitted psychiatric patients in the Royal Victoria Hospital, Netley, and also of a parallel series of 78 normal personnel of the Royal Army Medical Corps as controls. The distribution of the thyroid index in this series appeared to follow the pattern of that found by Reiss et al[9] in the psychiatric population of Bristol Mental Hospitals. Psychiatric casualties between the ages of 18 and 21 years showed a greater number of variations than controls of the same group, as illustrated in table I.

In tables I and II Robinson has shown that the mere occurrence of endocrine abnormality in thyroid function, as measured by the I^{131} uptake in the first hour and after 24 hours, can coexist with ordinary mental health. Conversely, Reiss et al[9] have demonstrated that the majority of mental patients of the average mental hospital population do not show deviations measurable by present methods. In nearly 300 cases investigated at St. Ebba's

TABLE II
Statistical Analysis of Table I

	Within normal range	Without normal range
Royal Army Medical Corps	68	10
Patients	97	34

Incidence of subjects falling within or without the normal range of thyroid index in Royal Army Medical Corps controls and psychiatric patients.
Chi square (d.f. = 4.318. Significant at $p = 0.05$. (Yates correction applied.)

Hospital during the last year, 65 per cent showed tracer results within normal variation; we also found that females showed results above normal in a significantly greater percentage than males.

Since the cases were in some degree selected, they are not strictly comparable with the series of Reiss et al.[9] None the less, all investigators found endocrine abnormalities, as measured by the same tracer and steroid techniques, in a significantly greater proportion of psychiatric patients than of normal controls. It was these observations that stimulated further inquiry into the possible use of endocrine methods of investigation and treatment, with the expectation that if any definite advance were made it would be on a very limited front. Both psychiatric patients and tracer apparatus are likely to be temperamental, and in order to avoid sources of error the following measurements were made: (1) the I^{131} uptake slope in the first hour; (2) the 24 hour uptake rate by a Ring counter specially designed for psychiatric patients; and (3) the 24 hour and 48 hour urine excretion rates.

Radioactive tracer estimations were performed under the supervision of Dr. W. W. Kay, of the Group Laboratory, making use of the methods employed by Reiss et al[9] and Haigh et al, except that the 24 hour uptake of iodine was checked against the 24 hour excretion rate. If the sum of excretion and uptake was over 100 per cent, the excretion value was preferred. The I^{131} tracer method measures only the rate of iodine uptake, and in order to secure a more adequate view of the activity of the thyroid, a fourth parameter measuring the production rate of thyroid hormone has been added. It is naturally difficult to know just what should be regarded as the normal range of variation, but the controls quoted suggest that we are at least fairly near the truth. The I^{131} uptake in the first hour (K) should be under 3.0, and for the sake of caution the normal 24 hour I^{131} uptake rate was taken as 25 to 50 per cent, instead of the more usual upper level of 40 per cent found in the literature. The normal range of I^{131} excretion was regarded as between 25 and 50 per cent. Ketosteroid excretion measurements were based on the method of Callow and Callow. The normal range in men varies from 9 to 21 mg. and in women from 7 to 15 mg. Experience in general medicine indicates how careful one must be in the interpretation of the significance of biochemical measurements. The normal blood sugar range is from 70 to 120 mg./100 ml., yet diabetics may function for long periods over the upper limit before showing clinical symptoms or signs. Similarly, it is possible to have a serum potassium level below normal a long time before the onset of flaccid paralysis (normal 3.6 to 5.1 M N or 16 to 20 mg./100 ml.). It is evident that normal ranges are not a bar to the onset of symptoms, and

TABLE III
Iodine Tracer Tests
Since December 1954

	Females	Males
Normal range	67 (55%)	125 (71%)
Above normal	47 (38%)	37 (21%)
Below normal	9 (7%)	15 (8%)

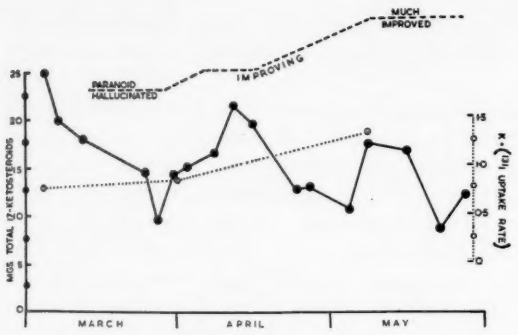

FIG. 1. Graph showing the fluctuation in ketosteroid output often seen in the more acute schizophrenic patient and the decline in these fluctuations associated with improvement in the mental state. Both tracer and ketosteroid results have become more normal as the patient spontaneously progressed.

abnormal values are certainly no guarantee of the presence of symptoms. We cannot yet speak of endocrine equilibrium in any exact sense, since we can measure only a few of the parameters of certain endocrine glands.

So far we have worked mainly on cases of schizophrenia and psychopathic personality in both adults and juveniles as being types likely to carry a high rate of constitutional abnormality. The majority of patients have been physically examined endocrinologically and have had both tracer and ketosteroid estimations, many with frequent repeating of tests. The main uses of these tests have been in prognosis and treatment.

During routine biochemical examination of the more recent cases, it was noticed that as patients improved clinically, there was also an increasing tendency for the tracer and 17-ketosteroid results to fall within normal ranges, even though the initial tests might not be considered to be more than borderline abnormal. This trend was seen with spontaneous remissions and in patients treated by electroconvulsive therapy, insulin, and amphetamine. An example of this observation is given in figure 1, which shows the fluctuation in ketosteroid output so often seen in the more acute schizophrenic patient and the decline in these fluctuations associated with improvement in the mental state. Both tracer and ketosteroid results have become more normal as the patient spontaneously progressed.

A preliminary report can be given concerning the relationship of steroid and tracer deviations to the prognosis with insulin coma therapy in 17 cases. In each case a tracer test with at least two total ketosteroid estimations, and often more, was done before insulin therapy was started. Independently a clinical prognosis and a prognosis based on the biochemical findings were given for each patient in regard to insulin therapy. The insulin course proceeded in the ordinary way, except that 17-ketosteroid estimations were done on Sunday, the only day on which the patient was completely free from insulin. After treatment, tracer and steroids were repeated. The clinical prognosis was based on the generally accepted criteria, including previous personality, duration of illness, mode of onset, maintenance of affect, and so forth. The biochemical prognosis was based on: (1) The clinical assessment of physical development and in particular of the gonads. Only macroscopically severe degrees of abnormality were considered. (2) The 17-ketosteroid excretion rate, an

increased excretion rate indicating increased adrenal function, and vice versa. (3) Thyroid activity, as measured by tracer and basal metabolic rate.

The outcome of the investigation was that, of the 17 patients, the clinical and biochemical prognoses substantially agreed and were correct in 10 patients. In 4 the clinical prognosis proved wrong and the biochemical right, and in 3 the clinical prognosis was correct but the biochemical wrong. For what it is worth in this small group, the biochemists are so far one up on the clinicians.

In general, it was evident that where 17-ketosteroid excretion was high and the thyroid tracer result low or average, the prognosis for insulin therapy was satisfactory. High thyroid tracer and low 17-ketosteroid excretion, or low results in both tests, were associated with poor insulin therapy results. Although some patients showed an initial rise of ketosteroid output, in the more successful patients ketosteroid levels tended to fall sometimes below normal range during the course, though the original level might be nearly regained after treatment. The success of insulin therapy in those patients having a high 17-ketosteroid excretion rate at onset seems consistent with the improvement gained by Broster after adrenalectomy in psychiatric patients with hyperadrenalism and with the temporary psychotic disorders seen after increased ACTH and cortisone administration. Altschule and others have put forward the view that success with insulin therapy is due to some degree of exhaustion of the adrenals. Our own small experience would tend to support this view. Equally, if the ketosteroid excretion is already low before treatment, it may be inadvisable to lower it further. The presence of physical immaturity, both in the body generally and in sexual development, was also associated with poorer results. If substantiated by the further work now proceeding, these last two observations would be consistent with my observation that in juvenile and adolescent schizophrenia it is unusual to obtain a good insulin coma result until after the age of 15 or 16 years, when the adrenarche is nearly complete and when the 17-ketosteroids are approaching adult levels. These remarks apply mainly to the more recent cases of schizophrenia and to results after treatment without follow-up.

Since it is clear that a number of different hormones can influence the function of the nervous system, it was thought advisable to concentrate mainly on discovering what their limitations and possibilities might be before giving full attention to any role they might possess in therapy. For this purpose, selected patients were given a physical endocrinological examination, tracer and 17-ketosteroids also being estimated when the patients were not on other forms of treatment. If the examinations were all negative and endocrine equilibrium was undisturbed, no further steps were taken except sometimes to repeat these tests, particularly if spontaneous remission was likely. If illness continued, an attempt was made to modify the function of the particular endocrine gland or glands that appeared to be abnormal by reason of the tests made, and then to correlate subsequent biochemical changes, if any, with the progress of the mental state.

The techniques employed are probably best illustrated by actual cases. For instance, a man of 29 years was admitted with a provisional diagnosis of schizophrenia, with gross thought blocking, stilted behavior, and obvious inadequacy both in affect and in social responses. He had been discharged from the Army in 1944 with a diagnosis of inadequate

personality, and in another hospital to which he was later admitted he was labeled schizophrenic. His background showed domination by his mother from early life, few friends, a quiet, rather withdrawn attitude, no interest in girls, and a general history of social inadequacy. He was clearly not a suitable candidate for insulin therapy, and he failed to respond to psychotherapeutic and rehabilitative measures. Because of his clinical inadequacy, and since his ketosteroid output in two specimens was at the accepted lowest normal level and the beta percentage was also low, he was given 20 mg. of diandrone daily. Strauss et al and Sands and Chamberlain have previously reported a good therapeutic response in similar patients. Over a space of three months the dose was raised to 60 mg., but there was only a very moderate mental response; the patient was more cheerful, but was still slow and inhibited. A few months later tracer results showed that thyroid iodine uptake was too low, but 17-ketosteroids were within the upper normal range. He was given thyroid extract, 1 gr. daily, the dosage being finally raised to 4 gr. The staff reported improvement in his slowness, conversation, and sociability after six weeks. This has been confirmed by his doctor, and the improvement has been maintained over the last seven months on 2 gr. of thyroid daily. It will be noted that first diandrone was given unsuccessfully on the basis of clinical and steroid findings only, but there is no doubt in the minds of those who have his daily care that the patient's mental improvement has resulted from the administration of thyroid. The schizophrenic aspects of his condition had already improved after his admission to the hospital, and the main difference after thyroid has been in the features that formerly made up his very schizoid, socially inadequate personality.

Patient L., 18 years of age, was referred from the Assize after assault and stealing. His father was aggressive and dominating, but his mother was self-effacing and a poor mixer, the pattern mainly inherited by the patient, who was sent away to boarding school when 6 years old. The patient described himself as seized by tension when frustrated, followed by a fantasy of seeing himself in a uniform, usually of a post-office messenger boy or a boy scout. He obtains the uniform by stealing or assault, dresses himself in it, experiences full sexual stimulation on looking at himself in a mirror, and then relief of his tension. He was treated psychotherapeutically for 13 months, but continued to be unsettled and was agitated and restless at times; during this period he stole a bicycle. I^{131} tracer tests indicated thyroid underfunction (E_{24} 64 per cent, E_{48} 67 per cent, K 0.85); serum cholesterol was 98 mg./100 ml. 17-Ketosteroids were in the upper normal range. Although he had been used to having other drugs and tablets, he improved on 2 gr. of thyroid daily, now being more confident, a better mixer, and able to sleep without sedatives. In the morning he was depressed for a time, but he has now lost this feeling and all interest in uniforms. Temporary reduction of the thyroid over 16 days resulted in some relapse, particularly in regard to homosexual thinking. Since the dose has been restored he has improved, his ideation is predominantly heterosexual, and he makes a more masculine impression. He will probably need thyroid indefinitely.

A different approach was used in a boy of 13 years, who was referred with a two and a half years' history of increasing nervousness and irritability, with laughing, gesticulating, and a habit of talking to himself. The parental management had been very ill balanced.

His birth had been a difficult one, and physically he showed much pubic hirsutism and undescended testes. When he was seen, his talk wandered inconsequentially and he had various mannerisms and seemed "odd" in a superficially adult way. He made no friends in the ward and was merely tolerated by the other boys and pushed around by them. His iodine tracer result was normal, but 17-ketosteroids were uneven and at times high. The fractionation of ketosteroids showed that dehydroisoandrosterone was increased, while androsterone was decreased. An attempt was made to normalize the ketosteroid metabolism by the use of chorionic gonadotrophin (Pregnyl), 1500 units daily intramuscularly, with the result shown in figure 2. Psychologically the patient appeared to show more initiative, to be able to stand up for himself, and to be mixing better socially. This change has been maintained for the last four months, and he has been discharged.

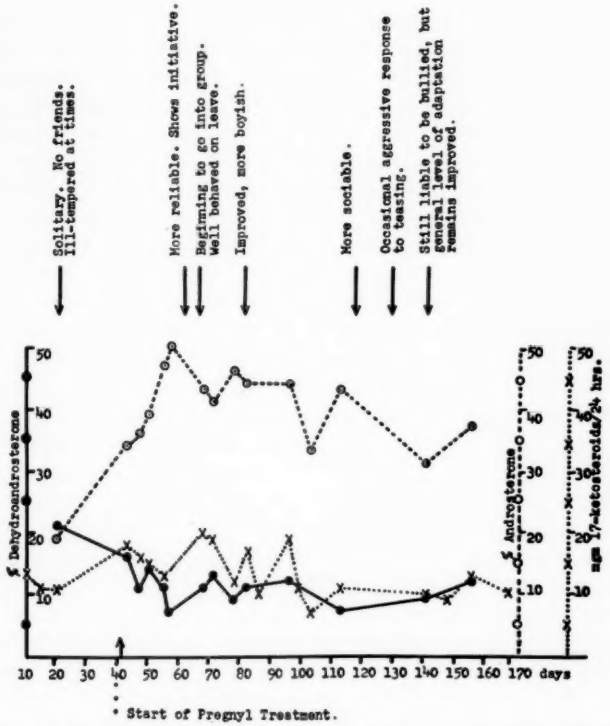

FIG. 2. Graph showing results of an attempt made to normalize the ketosteroid metabolism in one patient by the use of chorionic gonadotrophin (Pregnyl), 1500 units daily intramuscularly. Psychologically the patient appeared to show more initiative, to be able to stand up for himself, and to be mixing better socially.

Concerning testicular hormone, its applications would appear to be three: (1) in small doses for the stimulation of pituitary function; (2) in somatic immaturity with adrenal and testicular underfunction; and (3) as an anabolic stimulant where weight loss is severe in cases of hysterical and pituitary anorexia.

In the first category the following patient showed some benefit from the use of depot testosterone. A boy of 12 years, small in stature, shy by disposition, much indulged by his mother, was admitted to the juvenile department because of temper tantrums, truancy with refusal to attend school, complaint of pain in the stomach, and a feeling of suffocation and a lump in his throat. He was much teased at school. He had been very preoccupied with his health and was indifferent to sports, preferring solitary occupations. He was regarded as being in an anxiety state with physical and social immaturity. He adjusted to the hospital fairly well and somatic symptoms diminished, but he attacked his mother at visiting time. In view of his continuing instability he was investigated further. Intelligence proved average; the electroencephalographic record showed immaturity; genital and pubic hair development was backward; both thyroid tracer test and 17-ketosteroid output was low, suggesting pituitary underfunction. He was given Primoteston (a depot form of testosterone), 250 mg. weekly. About a week after the first injection he stated that he felt better, that he could run about more, and that he noticed he did *not* lose his temper, even when teased by others in the juvenile ward. Physically, he gained 11 lb. in two weeks and 1 inch in height during his stay; pubic hair began to grow and his penis and testicles increased in size. The school reported improvement in educational performance, his arithmetic results in the Southend test moving from 8 years, 5 months to 10 years, 7 months. The tracer level and ketosteroid output increased from low to average levels. He was discharged home recovered after 11 weeks in the hospital. It is felt that admission to the hospital and psychotherapy improved the anxiety symptoms, but the patient remained constitutionally immature and liable to relapse. His responses to stresses subsequent to five injections of Primoteston depot were greatly improved, and no further aggressive episodes occurred.

The following patient, a boy of 13 years with somatic immaturity and testicular and adrenal underfunction, may be considered as falling into the second group. He was chronically anxious and inadequate. In disposition he was shy, sensitive, and apt to be jealous of his siblings. He had stammered from 2½ years of age, was a chronic nail biter, and for a year avoided school by complaint of aches and ailments or truancy. Physically, secondary sex characters were absent, the penis was very small, and the testes liable to return back into the abdomen when the boy was lying down. Ketosteroid output was low (3.2 and 3.8 mg./24 hours), but the tracer result was in the normal range. The electroencephalogram was mildly abnormal, with marked instability on overbreathing. After five weeks of routine treatment with psychotherapy, education, and occupation, the patient was fairly settled in relation to the other boys, but he still stammered. He was given Primoteston, 50 mg. every three weeks, with some improvement in his stammering, but he became rather defiant and bullying. After two and a half months the Primoteston was doubled and given biweekly with diandrone, 10 mg. twice daily, because the ketosteroid output had remained low and the stammer relapsed. This resulted in a gain in the quantity but deterioration in the

quality of his language, and he could certainly swear without stammering. At this stage the 17-ketosteroid excretion rate had reached a plateau of 9 mg./24 hours. He became so rebellious, irritable, and aggressive, especially three days after the injections, that it was plain that he had been overdosed with testosterone, and he was taken off it, but diandrone was continued. On this regime he settled down and volunteered the observation that diandrone "made me not bother about my stammering so much." He gained 2 stones in weight in four months, his school performance improved, and he was discharged home much improved. This case indicates the effects of excessive testosterone medication mentally, even though the patient matured physically, whereas diandrone proved the more successful from the psychiatric angle, improving stammer and social performance.

In regard to the third indication, anabolic effects have already been obvious, but in anorexia nervosa there may be a special field for its use. A girl of 14 years was referred because of severe anorexia present since 1951. She was emaciated, had lost 3 stones in weight, and had the elderly look of the chronically starved. She was very unstable and immature emotionally, was childish, and at first just pecked at her food. The mother was tense and full of guilt and gave in to the daughter's every whim. The patient's hands were slightly cyanotic, her breasts were barely developed at all, and although much downy hair was present on the face, pubic hair was negligible. The thyroid tracer result was in the normal range (E_{4s} 44.1 per cent, K 1.35, I_t 3.06), but 17-ketosteroid excretion, at 3.7 and 3.0, suggested underfunction of the adrenals. Under chlorpromazine, 25 mg. three times daily, she was persuaded to start eating a little. She gained little weight on chlorpromazine, although emotionally she improved. After four weeks she was given Primoteston depot, 50 mg. intramuscularly weekly. She gained 4 stones in the next three months, moving from 4 st., 4 lb. on admission to 8 st., 5 lb. on discharge (fig. 3). She had an excellent appetite, regained her color, and lost the hair on her face, but developed pubic and axillary hair. She became lively and cheerful, and looked her age. The likelihood is that chlorpromazine enabled her to take some food, so that the anabolic action of testosterone could take effect and eventually create more of an appetite. 17-Ketosteroids rose to 6.7 mg. (in the normal range for this age).

By way of a tailpiece to the use of testosterone, I might mention the 30 year old married man who, having suffered from psychogenic impotence and fetishism for 18 months, was relieved in the course of three weeks by testosterone, 50 mg., and diandrone, 10 mg., both intramuscularly daily, eventually achieving normal sex relations with his wife four times in 24 hours.

There are times when the reverse situation occurs. It may be necessary to control actual or relative precocity, as illustrated by a 14 year old boy admitted on probation after indecent assault of a 10 year old girl, and who, a month previously, had had homosexual behavior with another boy. In his home, which was otherwise satisfactory, the subject of sex was completely taboo, and he was quite uninstructed in it except through school acquaintances of the wrong type. In consequence he felt handicapped in associating with schoolmates on equal terms. Contrarily, he felt that undressing in front of other boys was embarrassing, though he had exposed himself to others in his offenses. Physically, his genitals and pubic

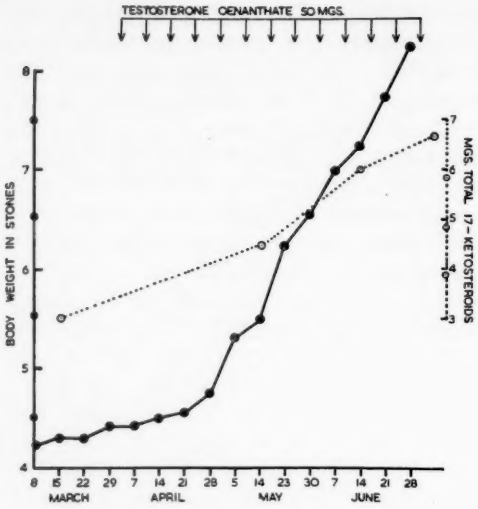

FIG. 3. Graph showing weight gain in one patient given Primoteston depot, 50 mg. intramuscularly weekly.

hair were most precociously developed, and he masturbated three to four times a week. In view of his history, and because of the disparity between his physical and his psychologic sexual development, he was started on stilbestrol, 1 mg. daily orally, which was increased by 1 mg. weekly to 4 mg. After two weeks he said his sexual urges were diminishing: "I feel I am able to control myself," and again: "I do not feel filthy now." He masturbated only once in two and a half weeks, and began to be less shy about undressing. Psychotherapeutic discussions were productive; after five weeks, reduction of stilbestrol was gradually effected and it was omitted after seven weeks without relapse. Estimations of thyroid activity by tracer tests and of 17-ketosteroid excretion were normal before treatment was started, though 17-ketosteroids were subsequently depressed by stilbestrol. The thyroid tracer results remained in the normal range. The boy may need further occasional short courses of estrogens until balance is achieved between physical and psychosexual maturity. He departed much improved, to return home and to his school.

The patients discussed have been generally assisted by treatment, and the results of biochemical investigations have shown some value in prognosis. There is another side. A 15 year old girl was admitted from another hospital, having developed a schizophrenic illness during cortisone therapy for acute articular rheumatism and carditis. First depressed, she then became confused and restless and talked of being in heaven and hearing angels. She displayed mannerisms, rocked to and fro, smiled incongruously, talked nonsense, used neologisms, and was incontinent. She began to improve after three weeks, and eventually emerged as a shy, quiet type of girl who had no further difficulty. When her psychiatric disorder settled, there was some correlated physical improvement, though exercise tolerance continued to be low. She returned to the original hospital and has since been given a post on the staff within her physical capacity. No previous mental instability was known.

A borderline defective girl of 15 years had had a schizophrenic attack with some hysterical traits. She had also been reported to have what were described as periods of silent withdrawal for about a week since the menarche, which was at 12 years. In the hospital, phases of apathy and poor cooperation appeared to be associated with her menstruation. During her stay she was given diandrone, 10 mg. daily orally, because of inertia, slowness, and lack of initiative, but after two days she became noisy, overactive, aggressive, and abusive, to the extent that transfer to another ward was necessary. The reaction subsided after five days, and thereafter the patient settled down and her behavior was consistently good. 17-Ketosteroids were low for her age.

Both these last patients broke down into short psychotic illnesses when given adrenal steroids in adolescence, though the dosage was quite average. Both were immature in different ways, and appear to have been unable to adapt to a further increase of adrenal steroids above that which normally takes place in adolescence.

The response of chronic cases needs further investigation, but it is already evident that many such patients become highly resistant to endocrine administration, and the situation is the opposite of the patients just mentioned. A youngster of 13 years, a boy with a history of schizophrenia since early childhood, having a somewhat immature physical sexual development, normal thyroid and basal metabolic rate results, but fluctuating 17-ketosteroid output, was given 50 to 150 mg. of testosterone depot injections over seven months without any mental reaction at all, though physical maturation improved. It was noticed that this boy had a considerable capacity for disposing of testosterone, since injections of 150 mg. depot did not appear to raise the 17-ketosteroid output for more than six days, though other patients showed a rise for 16 days or more (fig. 4).

Another 15 year old boy with a four year history of schizophrenia that had defied all forms of therapy, including a standard leukotomy, was given 1000 mg. of testosterone in depot form, guarded with 20 mg. of stilbestrol, daily for 10 days. Clinically, he was quite unmoved for better or worse by this large experimental dose. His 17-ketosteroid output, which usually fluctuated from 6 to 11 mg., moved to 21 mg. the day after injection, was

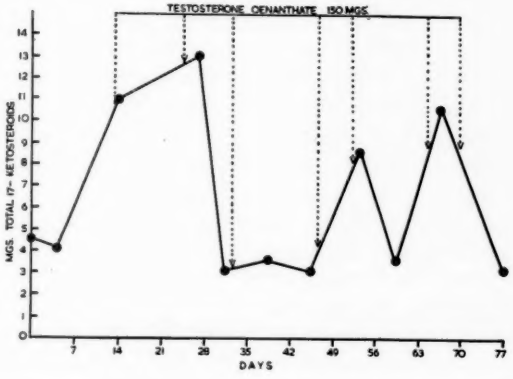

FIG. 4. Graph showing considerable capacity of one patient for disposing of testosterone. Injections of 150 mg. depot did not appear to raise the 17-ketosteroid output for more than six days, though other patients showed a rise for 16 days or more.

17.6 after a week, and three days later was only 4.5 mg., no doubt under the continuing suppressive influence of stilbestrol.

COMMENT

Certain observations can be made from the work done so far. Regarding the incidence of normal and abnormal thyroid and steroid estimations, the reports of Reiss et al[8, 9] at Bristol have been largely confirmed, as has also their observation that normal findings in a recent case are usually of good prognosis, and that in chronic patients the thyroid and adrenal functions have again become stabilized within normal limits. Concerning insulin coma therapy, it is well known that for a number of years the diagnosis of early schizophrenia of less than two years' history has been practically synonymous with the administration of insulin coma, with a fair degree of success. However, not all recent cases respond to insulin, and obviously much time, effort, money, and inconvenience would be saved to all concerned if it were possible to be more selective. Insulin coma therapy itself is an undoubted stress, and in the small group of patients investigated there were some who before treatment did not show the usual evidence of increased adrenal cortical function with raised ketosteroid output. Such patients may also show immaturity in primary and secondary sexual development. These patients were always associated with an early history of considerable stress in childhood and early adolescence, and it would appear that their reactions to stress were either inadequately developed or exhausted. Those who are familiar with the more drastic methods of physical treatment know that some recent schizophrenic patients seem unaltered by electroconvulsive therapy, insulin comas, or leukotomy, and they come to be thought of in terms of dementia praecox rather than of schizophrenia. At present I can only say that they are very like the failures in the present small series. By contrast, patients showing signs of raised adrenal cortical function, with normal or even depressed thyroid activity, did well. In normal persons ketosteroid output varies little, but in active cases of schizophrenia there is often much fluctuation.

Twenty to 25 patients have been given androgens, either by daily injections of testosterone or by less frequent use of androgen depot preparations. Both testosterone and diandrone are now available in depot form. The duration of their effect is not as long as has been claimed and in some cases may be less than a week, even with fairly high dosage. In most patients the effect will not last longer than 16 days and should be correlated with weekly ketosteroid estimations until the duration is more accurately known. None the less, for prolonged androgenic action such preparations are an improvement.

Clinically, testosterone has improved these adolescent patients who were emotionally, socially, physically, and biochemically immature, who have felt inferior, become anxious, and shown behavior disorder on this basis. Even if occasional tempers have been shown in the past, testosterone does not worsen such aggression so long as the patient is basically inadequately immature, though individual regulation of dosage is needed, since overdosage can swing even these patients into an irritable, aggressive phase. In the immature adolescent it has not provoked any strong overt signs of sexual activity. In older patients it can stimu-

late much sexual thinking and fantasy, in addition to a sense of greater energy and mild euphoria. Homosexuals cannot be changed to a more masculine attitude. In most of them, testosterone merely accentuates the homosexuality. In general, its action is to increase the quantity of the sex drive without in any way altering its main direction. There are patients who have both homo- and heterosexual qualities, and in those in whom the heterosexual activity is predominant it can help maturation, particularly if environment is also suitably adjusted.

The adrenal androgen, dehydroisoandrosterone (diandrone), has an action similar to that of testosterone in promoting increased confidence, activity, and at times aggression, but it seems to have little stimulating action on physical maturation of sex organs and characters or an effect on sexual fantasies, or any anabolic effect. It can provoke aggression and is clinically indicated when the immaturity is limited to social and emotional fields, such as was described in previous reports. We know from papers by Widdowson and others that chronic stress can impair physical and mental development in childhood. It is in persons of this type, who have subsequently broken down in adolescence and early adult life, often under quite ordinary strains, that androgens have a sphere of usefulness in raising the threshold of resistance to stress. I have seen such youngsters "grow up" both physically and mentally under the single or combined use of these androgens.

When gonadal and psychosexual development is precocious, leading to overactivity, tempers, undue masturbation, sexual assaults, and homosexuality, it may be necessary to depress sex drive and delay further sex maturation until the patient is more mature in other ways. Stilbestrol and Dimenformon have both proved effective and, when linked with psychotherapy and social supporting measures, have kept the immature and the psychopathic person out of further trouble.

Although some reference has been made to hormonal influences of therapeutic value, the first requirement is to discover more about their relationship to the nervous system and about their own normal variation and to improve biochemical measurements. From the present series of patients tested, one can say that present biochemical methods are of value, particularly if frequent repetition and long term studies are possible. There is still too much wastage, partly because of imperfections of technique and partly because these methods, originally developed for use in general medicine, need further modification before they can be fully applied to psychiatric patients. It is probable that it will be necessary to arrange for tracer tests to be done under similar conditions to the basal metabolic rate, or with the use of sleep, to exclude factors at present causing occasional inaccuracy. Even now, when combined with clinical assessment, these methods can in some cases give information of prognostic value or indicate a line of treatment that might have been missed on clinical psychiatric grounds alone. For the most part, hormonal action is linked with major factors in maturation and constitutional function, e.g., growth, reproduction, nutrition, and the homeostatic mechanisms of the nervous system. There is no evidence as yet that hormone action has much part to play in the symptomatic treatment of any of the common syndromes of psychiatry per se. Indeed, hormones may aggravate a neurotic or psychotic reaction by further disorganizing the individual's endocrine requirements, so that hormone

imbalance becomes a stress in itself. The cases we have studied suggest that the role of hormones in relation to disorders of the nervous system is not so much in bringing symptom relief as in the correction of the chronic deviations of personality development that underlie so many psychiatric disorders. These come to light when physical methods clear up the more acute manifestations, or during the process of psychotherapeutic investigation, and one is left with what is sometimes described as a "vulnerable" personality, labeled perhaps as predominantly schizoid, depressive, obsessive, or psychopathic. These personality deviations are the joint result of heredity and earlier stresses, even from childhood. At puberty they are usually still in a developing and modifiable stage, and the sample patients discussed suggest that investigation and treatment at this stage may be the most rewarding.

Endocrinology and psychiatry both suffer a history steeped in controversy, with flashes of success and many failures. On the evidence available, there is nothing at this stage to warrant the deduction of firm conclusions on the relationship of endocrines to psychiatric disorder, but one only begins to see some indication of what the endocrine role will be. The standard approach of clinical and biochemical correlation, succeeded by such therapeutic intervention as has seemed indicated, has been reported here. There is no indication that the endocrine method will ever be a complete treatment for any psychiatric disorder, but by attention to this hitherto rather obscure field we may be able to improve considerably our patients' ability to adjust to stress, and to supplement usefully our efforts to do precisely the same thing from psychotherapeutic angles. In short, endocrinology may be able to increase the patient's potentiality for normal adaptation, but it will continue to be necessary for the psychiatrist to show him how to use it.

SUMMARY

A reassessment has been made of the function of the endocrine system in relation to various psychiatric states. Investigations have been performed, chiefly on the adrenal and thyroid activity of over 300 juvenile and adult psychiatric patients. A preliminary report has been given concerning the relationship of steroid and tracer deviations to the prognosis of insulin coma–treated patients. Selected cases are described, illustrating the influence of different hormones on the nervous system. Some tentative conclusions have been drawn on the possible role of endocrines in therapeutics.

ACKNOWLEDGMENT

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RESUMEN

Se ha vuelto a justipreciar la función del sistema endocrino en relación con varios estados

psiquiátricos. Las investigaciones se realizaron principalmente, sobre la actividad suprarrenal y tiroidea de más de 300 pacientes psiquiátricos jóvenes y adultos. Se ha dado a conocer una comunicación preliminar sobre la relación entre los esteroides y las alteraciones en el curso de los elementos radioactivos en cuanto al pronóstico de los pacientes tratados por medio del coma insulínico. Se describen los casos seleccionados, ilustrando la influencia de las diferentes hormonas sobre el sistema nervioso. Se han deducido algunas conclusiones provisionales sobre el posible papel de las glándulas endocrinas en terapéutica.

RESUME

On a fait une nouvelle évaluation de la fonction du système endocrin par rapport à divers états psychiatriques. Des recherches ont été faites principalement sur l'activité surrénale et thyroïde de plus de 300 patients psychiatriques, jeunes et adultes. Un compte rendu préliminaire a été présenté concernant le rapport des déviations des stéroïdes et des corps marqués au prognose des malades traités par l'insuline coma. Des cas choisis sont décrits, montrant l'influence de différentes hormones sur le système nerveux. On a tiré des conclusions possibles sur le rôle probable des glandes endocrines en thérapeutique.

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Endocrine Concomitants of Certain Physical Psychiatric Treatments*

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When studying endocrinological psychiatry one finds that contrary to previous conceptions that have always tried to connect hormone action with various psychiatric syndromes, there is no specific correlation between any particular endocrine disease and any special psychiatric disorder, and, conversely, mental disturbances can be accompanied by a multitude of endocrine deviations.

The great majority of clinically recognizable and intermediate endocrine disturbances have no primary bearing on the development of mental disease. However, when the individual is subjected to various precipitating stress conditions and has to become adjusted to them, it is then that the role of the endocrine is decisive. Such adjustment is possible only as long as the endocrine equilibrium is in a state to guarantee a sufficient width of adaptation. In many instances, however, the precipitating factors can bring the endocrine equilibrium into disorder, either directly or via the resulting mental stress. The outcome of such a situation can consist of various disturbances in the somatic function and can also be an important link in the physiopathology of mental breakdown. When reviewing the whole field one realizes that a great number of quite different stress conditions can precipitate various psychiatric disturbances, according to the personality pattern of the individual, which are accompanied by endocrine deviations that often can be analyzed by our still rather primitive methods of endocrine analysis. The present scope of psychoendocrinology has recently been reviewed by the author.[1]

It is interesting that a great number of treatment procedures in psychiatry consist in the application of more or less standardized severe stress conditions. When comparing the multitude of the possible precipitating stress conditions with the stresses applied therapeutically, one may best liken the situation to the casting out of devils by Beelzebub.

When studying the development of mental breakdown and disease and some of the treatment procedures, it is interesting to investigate the endocrinological concomitants. This is already being studied by us with the help of the few reliable methods that are at our disposal in clinical endocrinology. In order, however, to get an idea about the principal directions in which certain applied stress conditions influence the endocrine system, we have to resort to animal experiments.

Investigations on animals can give us some idea of the complexity of the various changes

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* Based on a paper read at the Quarterly Meeting of the Royal Medico-Psychological Association, London, Nov. 9, 1955.

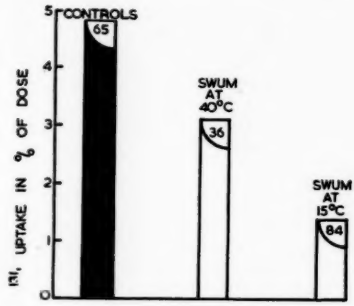

FIG. 1. I^{131} uptake by thyroids of male rats after swimming for 15 minutes.

in the endocrine equilibrium that occur during and after stress. However, we have to be extremely careful when making deductions from such experiments about endocrine changes produced on patients under stress conditions or physical treatment. Investigations on animals are always carried out on an object in which the initial condition of the endocrines is well circumscribed and in a situation where plenty of controls are available and statistical

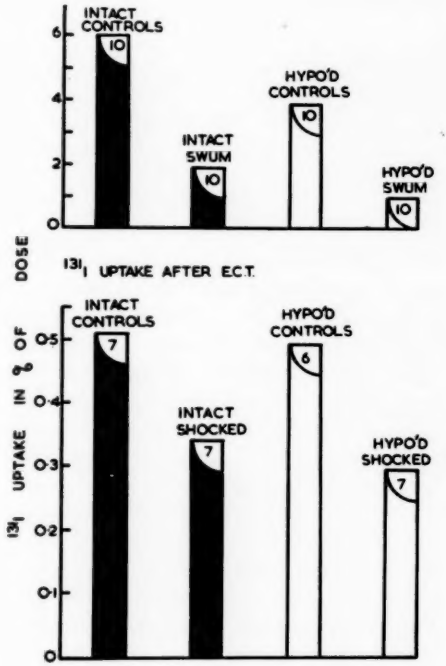

FIG. 2. I^{131} uptake by thyroids of intact and hypophysectomized male rats after swimming at 15 C. and after electroconvulsive therapy.

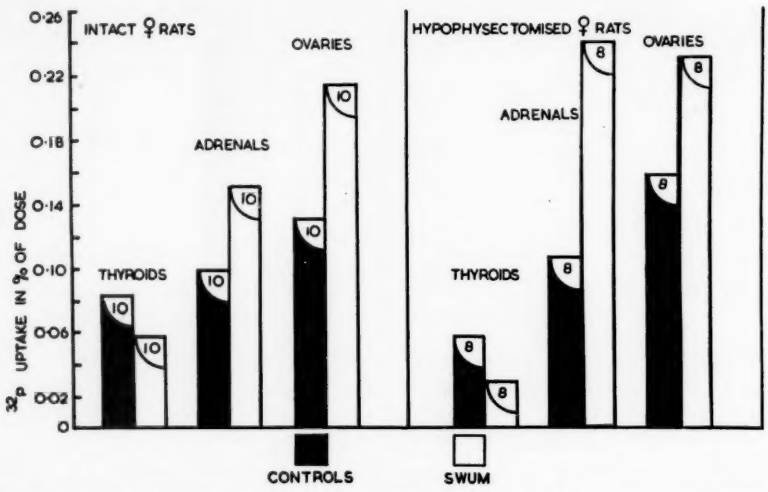

FIG. 3. P^{32} uptake by various glands of intact and hypophysectomized female rats after swimming in water at 15 C. for 15 minutes.

evaluation can be done on the basis of unbiased samples. Similar statistical evaluations on human beings are only too often valueless since the authors do not realize that their samples are biased and that, for example, the same stress condition will have an entirely different effect on someone whose adrenals or thyroid is not working sufficiently. I would go so far as to say that it is completely impossible to reproduce in an investigation on any animal exactly the manifold variations possible in the human hormone equilibrium. Only long term investigations on individual patients can bring us any further. The results of animal experiments point only to some basic laws in the endocrine regulatory mechanism and show the direction in which changes in the human organism might be expected under certain conditions.

Inspired by the observation of various endocrine changes and reactions seen in patients, my co-workers (Brimblecombe, Badrick, J. Reiss, Wyatt, and Redman) and I have been trying for several years to understand more about the changes that occur in the hormone equilibrium after various stress conditions.

Contrary to the general belief that all the acute changes found after stress are mediated by the pituitary, and particularly the pituitary adrenal cortex axis, it appears from our own investigations that in fact, many acute stress reactions are independent of the pituitary; also they are not solely restricted to the adrenal cortex. For instance, figure 1 shows that swimming in cold water for 15 minutes reduces the thyroid activity, as expressed by the I^{131} uptake, by about 70 per cent, whereas less stress, such as swimming in warm water, reduces the I^{131} uptake by only about 30 per cent. Figure 2 illustrates that the thyroids of hypophysectomized rats show similar changes after swimming. One can also see in figure 2 that the thyroid activity is reduced 30 minutes after a single electroshock treatment and

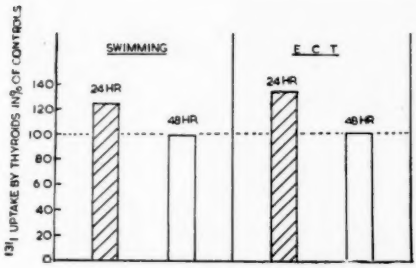

FIG. 4. I^{131} uptake by thyroids of male rats 24 and 48 hours after swimming or electroconvulsive therapy.

that there is no difference in this direction between the reaction of intact and hypophysectomized animals.

However, after acute stress there is considerable change not only in thyroid activity, but also in the activity of the adrenals and, to a certain extent, of the ovaries. Figure 3 shows that the P^{32} uptake rate of the thyroid is considerably decreased after swimming in cold water, while the P^{32} uptake rates of the adrenal and ovary are significantly increased, but identical changes also occur in animals previously deprived of the pituitary. Supported by some further results after adrenalin treatment of animals, we reached the conclusion that the acute stress effect on the hormone equilibrium is to a considerable part due to the mobilization of vasoconstrictor substances.[2]

It seems that the action of the pituitary anterior lobe after stress is more in the manner of a regulating response of the lobe to the changes occurring under acute stress. For instance, 24 hours after swimming or after electroshock, the I^{131} uptake of the thyroid is significantly increased (fig. 4).

It was most interesting, in this connection, to investigate the hormone content of the pituitary. We investigated the pituitaries of stressed animals for their ACTH content by the ascorbic acid depletion method. The thyrotrophic hormone content of the pituitary was investigated by the method recently worked out by Reiss and Wyatt[3] based on the I^{131} uptake by the thyroid of newborn animals.

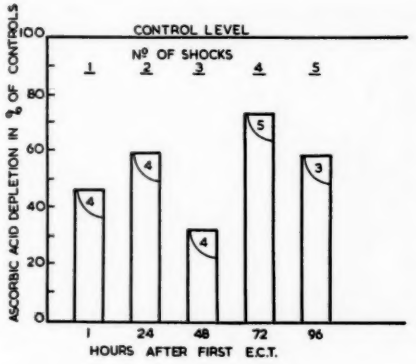

FIG. 5. The effect of repeated electroconvulsive therapy on ACTH content of fresh rat pituitaries.

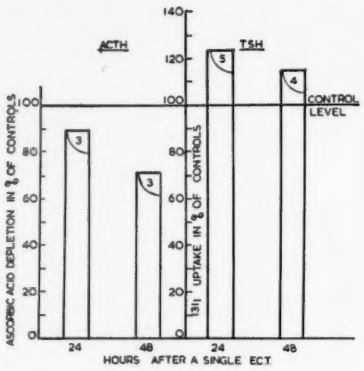

FIG. 6. The effect of electroconvulsive therapy on the ACTH and thyrotrophic hormone content of fresh rat pituitaries.

Figure 5 shows how the ACTH content of the pituitary is continuously kept down by daily electroshock treatment, and figure 6 shows that in the same pituitaries in which the ACTH content is decreased, after a single electroconvulsive therapy treatment the thyrotrophic hormone content is significantly increased.

The action of insulin coma on the ACTH content of the rat pituitary seems to be quite different. After one single coma the ACTH content was found to be increased for the first three days and decreased from the fourth day onward (fig. 7). However, the insulin action on the pituitary endocrinology and the endocrine function of the pituitary is variable and very involved; it is at present still the subject of our intensive investigations.

After investigating the effect of such stress conditions on some endocrine functions, it was of some interest to investigate the action of a drug that is supposed to protect against stress, chlorpromazine. We were rather surprised to find to what considerable degree this drug influences the hormone equilibrium. After four days' treatment with chlorpromazine, the thyroid weight was decreased, but its I^{131} uptake rate was significantly increased, while the adrenal cortex weight was increased and the ovary weight considerably decreased; also, thyroid function was reduced, as was concluded from the lower uterus weight (table I).

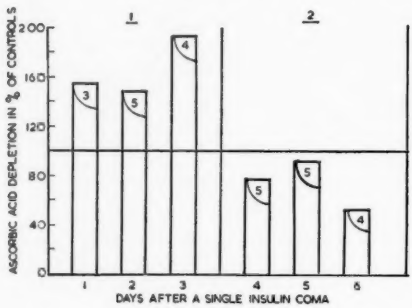

FIG. 7. The effect of insulin coma on the ACTH content of fresh rat pituitaries. Comparison of two experiments.

TABLE I

Influence of Chlorpromazine on Hormone Equilibrium

Treatment	No. of rats	Change in body wt. (Gm.)	Wt. of thyroids		I^{131} uptake by thyroids in % of dose (18 hr.)		Wt. of adrenals		Wt. of ovaries		Wt. of uterus		Wt. of pituitary	
			*	†	*	†	*	†	*	†	*	†	*	†
Controls	8	+4	13.2±2.6		21.1±3.3		59.3±8.9		61.4±9.7		327±103		10.6±1.5	
Chlorpromazine, 6 mg. 2 times daily for 5 days	7	−18	10.6±2.0	−20‡	29.6±7.6	+40‡	75.5±10.7	+27§	41.8±12.3	−32§	249±66	−24	10.3±1.8	−3

* Mean±standard deviation (mg.).
† Per cent change from controls.
‡ Denotes significant change at $p = 0.05$.
§ Denotes significant change at $p = 0.01$.

Investigation of the pituitary anterior lobe of animals treated with one injection of chlorpromazine revealed a considerable increase of the ACTH content (fig. 8).

If one considers how manifold are the various causes for the disturbance of the adaptation width and of the hormone equilibrium of a mental patient, it will be realized how very much a gamble some of the treatment procedures are. The same stress condition can repair in one case and aggravate in another some disturbances of the hormone equilibrium.

The main purpose of psychoendocrine research will have been achieved once the endocrine changes accompanying spontaneous improvement or improvement after various treatment procedures have been exhaustively elucidated. Only then could one try to imitate either the working of the body's own regulatory mechanism or the changes produced at present by dramatic therapeutic methods. A modest beginning has been made in this direction.

However, one has to bear in mind that even if it should be possible one day to improve acute psychiatric conditions by rational hormone therapy, it would not necessarily mean

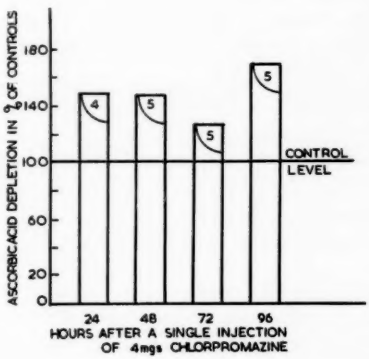

FIG. 8. The effect of chlorpromazine on ACTH content of fresh rat pituitaries.

that such an approach would be able to influence chronic conditions any more satisfactorily than is possible with the most dramatic treatment procedures used at present. When a pathologic thought content has become fixed in the brain, even a completely normal hormone equilibrium—and we have seen repeatedly that the latter can normalize itself spontaneously in the course of years—has very little influence on the psychopathologic phenomenology. However, one never knows whether we will not be able one day to penetrate the protective mechanisms that make possible the fixation of pathologic thought content. This is obviously also a mechanism, the functioning of which is the basic condition for the ability of the brain to learn and accumulate experience.

The question is whether such a mechanism might be connected to some extent with the blood brain barrier. We have lately found some interesting facts concerning the role of the blood brain barrier in the action of thyroid hormones on the brain metabolism of adult rats and rabbits. We have investigated for many years the action of thyroid hormone on the brain metabolism, but have been unable to demonstrate an increase in the brain oxygen consumption, even after treatment for seven days with high doses of thyroxin or thyrotrophic hormone at a time when the oxygen consumption of the liver and of the other organs was very considerably increased.

We then tried to investigate the action of thyroid hormone on the brain oxygen consumption of newborn rats and to our surprise found that in these animals, a significant increase in the oxygen consumption of the brain was regularly produced by thyroxin, triiodothyronin, and thyrotrophic hormone.[4] It was assumed that the brain blood barrier of these animals is not yet properly developed, and therefore the oxygen consumption of the brain can be raised. In further experiments we tried to see whether it is possible to break through the brain blood barrier of adult animals, making possible the increase in the oxygen consumption of the brain by thyroxin. After many vain attempts, we frequently succeeded in doing so by pretreating animals for several days with pentobarbital (Nembutal). After this pretreatment the brain oxygen consumption of adult animals could also be considerably raised.

When studying these results it was tempting to speculate about the parallelism between the conditions under which the thyroid hormone can enter the brain of the young animal and the ease for education, learning, and the acquisition of normal or pathologic ideas by the young human brain. We were also tempted to ask whether the existence of a brain blood barrier is not similarly connected with the entering of some hormones in the brain, altering its metabolism, and with the fixation of some thought processes. Such considerations were also accompanied by consideration of the various forms of psychiatric abreaction. Of course, we still know very little about the nature of the brain blood barrier. However, should there be any probability in the evaluation made of the facts mentioned above, procedures that help us to break through the brain blood barrier would, in proper combination with biochemical and psychologic procedures, become of great therapeutic value in the future.

SUMMARY

A disturbance of the endocrine equilibrium becomes decisive in the development of mental disease only when the individual is subjected to various precipitating stress condi-

tions. Then, owing to the restriction in the width of adaptation, the individual can break down and develop mental illness in accordance with the premorbid personality pattern.

Precipitating stress conditions and various standardized treatment procedures alike can produce changes in the endocrine function, which ought to be specified in order to understand success or failure in therapy.

Some basic changes in the endocrine function produced by various treatment procedures were studied in animal experiments.

The role played by the pituitary in acute stress conditions has been overestimated. Many acute stress reactions of the ductless glands are independent of the pituitary and are also not restricted to a change in the adrenal cortex function.

The uptake of radioactive phosphorus after electroconvulsive therapy, or other stress, is decreased in the thyroid but increased in the adrenal cortex and ovary. Identical changes occur in both normal and hypophysectomized animals.

The action of the pituitary anterior lobe after stress is more a regulatory response of the gland to the changes occurring during acute stress. One electroshock decreases the ACTH content of the pituitary and increases its thyrotrophic hormone content. One insulin coma seems to increase the ACTH content of the pituitary anterior lobe.

Chlorpromazine influences the hormone equilibrium to a considerable extent. After one injection, the I^{131} uptake rate of the thyroid is increased, adrenal cortex weight increased, ovary weight decreased, and the ACTH content of the pituitary increased.

A possible correlation between the existence of a brain blood barrier and the homeostasis developed in the brain to a higher degree than in other organs and the fixation of normal and pathologic thought is being discussed.

RESUMEN

Un trastorno del equilibrio endocrino puede desencadenar una enfermedad mental, sólo cuando el individuo está sometido a varios estados de stress que la precipiten.

En animales de experimentación se estudiaron algunos cambios básicos de la función endocrina, producidos por distintos tratamientos. Se ha sobreestimado el papel que juega la hipófisis en los estados agudos de stress.

La captación de fósforo radioactivo después de la terapia electroconvulsiva o de otra forma de stress, está disminuida en el tiroides, pero aumentada en la corteza suprarrenal y en el ovario. Ocurren cambios idénticos tanto en los animales normales como en los hipofisectomizados.

La acción del lóbulo anterior de la hipófisis después del stress es más que nada una respuesta reguladora de la glándula a los cambios que tienen lugar durante el stress agudo.

Se trata sobre la posible correlación entre la existencia de una barrera hematocefálica y la homeostasis cerebral, desarrollada en mayor grado que en otros órganos, y la fijación del pensamiento normal y patológico.

RESUME

Un trouble de l'équilibre endocrin n'est concluant dans le développement de la maladie

mentale que lorsque l'individu est soumis à certaines conditions de stress précipitées. Certains changements fondamentaux de la fonction endocrine produits par divers procédés thérapeutiques ont été étudiés chez des animaux d'expérience. Le rôle joué par l'hypophyse dans les états de stress aigus a été exagéré. La teneur en phosphore radio-actif après thérapeutique electroconvulsive, ou autre stress, est réduite dans la thyroïde mais augmentée dans le cortex surrénal et l'ovaire. Des changements identiques prennent place tant chez les animaux normaux que ceux ayant subit une hypophysectomie. L'action du lobe antérieur de l'hypophyse après le stress est plutôt une réaction régulatrice de la glande aux changements prenant place au cours du stress aigu. On discute la corrélation possible entre l'existence d'une barrière sanguine du cerveau et de l'homoéostasie qui se développe dans le cerveau à un degré plus élevé que dans les autres organes et la fixation de la pensée normale et pathologique.

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Plasma Corticoids in Psychiatric Illness

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Reduced responsiveness to a wide variety of stimuli has been observed in patients with schizophrenia. This change may include altered tolerance to chemical and endocrine stimulation, as demonstrated by a reduced reaction to insulin, epinephrine,[1] and histamine.[2] Various physiologic considerations bearing on adrenal function in patients with mental illness have been discussed by others.[3, 4, 18] Evidence has been presented by Pincus and collaborators to show that the reaction of the psychotic patient to certain stressful situations is abnormal.[5] An abnormal pattern of urinary 17-ketosteroid excretion has been observed in patients with chronic schizophrenia.[6, 7] A reduced response to corticotropin injection also has been demonstrated in patients with acute and chronic schizophrenia.[5, 8] Opinion is divided regarding the state of function of the adrenal gland in patients with mental illness. In a recent study of plasma 17-hydroxycorticoids in patients with chronic schizophrenia, Bliss et al[19] found no evidence of impaired adrenal function nor an abnormal response to ACTH injection.

The present study was undertaken to compare the state of adrenal function in male patients with acute mental illness, mainly schizophrenia, with that of a healthy group of male subjects of similar age. Blood plasma corticoid values were used as a basis for this comparison. The total fasting, free reducing plasma steroids and hydrocortisone-like compounds were estimated repeatedly on this group of patients. The plasma corticoid response to an infusion of ACTH was also determined repeatedly and compared to the response of healthy subjects. In addition, the plasma corticoid response to a standard oral test dose of cortisone was measured and compared to that obtained in healthy subjects. An effort was made at the same time to determine whether the blood corticoid levels could be correlated with a series of arbitrarily chosen psychiatric signs and symptoms.

METHODS AND PROCEDURES

The patients used for this study were chosen from the inpatient psychiatric service at the Veterans Administration Hospital, Hines, Ill. No effort was made to obtain a homogeneous group from the diagnostic standpoint. It was sufficient that the patient be acutely ill and available for testing. Sixteen patients were accepted for the study. Some of these had been in the hospital for several weeks to a few months before the study began. Others

Funds from the Schweppe Foundation contributed partial support to the laboratory work presented in this study.

TABLE I

Summary of Psychiatric Patients

Patient	Age, yr.	Race	Marital status	Diagnosis	Days in hospital before study	Period of study, days	Treatment during study	Manner of discharge
1	42	W	D-M	Schizophrenia, affective	23	93	ICT*	Trial visit
2	32	W	S	Schizophrenia, paranoid	15	94	None	Trial visit
3	31	W	S	Schizophrenia, paranoid	96	162	EST†	Continued hospitalization
4	35	N	Sep.	Schizophrenia, paranoid	3	162	EST	Continued hospitalization
5	40	W	S	Schizophrenia	2	154	ICT	Continued hospitalization
6	25	W	S	Schizophrenia, catatonic	247	99	EST	Trial visit
7	28	W	M	Schizophrenia, catatonic	23	93	EST	Maximum hospital benefit
8	46	W	M	Depressive psychosis	60	43	ICT	Against medical advice
9	38	W	S	Schizophrenia, paranoid	20	60	EST	Maximum hospital benefit
10	43	W	S	Passive aggressive personality	26	160	None	Continued hospitalization
11	65	W	S	Involutional psychosis	7	129	EST	Maximum hospital benefit
12	28	W	S	Schizophrenia, paranoid	122	130	ICT	Trial visit
13	31	W	S	Schizophrenia, undifferentiated	124	43	None	Trial visit
14	58	W	M	Involutional psychosis	7	129	None	Continued hospitalization
15	24	W	S	Schizophrenia, paranoid	43	74	EST	Against medical advice
16	34	N	D	Schizophrenia, paranoid	174	74	ICT	Against medical advice

* Insulin coma therapy.
† Electroshock therapy.

were used for the study as soon as admitted. A few patients were discharged after a brief period of study, while others are still hospitalized here or elsewhere. Some of the chronologic and clinical data concerning these patients are shown in table I. The patients were predominantly schizophrenic, but 2 (no. 8 and 14) were suffering from agitated depression, 1 (no. 11) from retarded depression, and 1 (no. 10), who presented a passive aggressive personality, came to the hospital with severe headaches and some paranoid trends subsequent to an episode of dissociation; patient no. 1 was in an excited schizophrenic state, which probably could be best described as a schizoaffective episode. Two of the patients (no. 7 and 11) were malnourished due to their psychiatric illnesses.

These patients had no special instructions, nor were restrictions placed on management except those absolutely necessary for collecting blood specimens. For example, breakfast was delayed a half-hour on days when fasting blood specimens were obtained, and the patients were necessarily taken off other programs when being given infusions. Treatment of each patient was in accordance with the best medical judgment of the individual physician. The therapeutic activities program was utilized as appropriate in each case, and supportive psychotherapy was given freely. In addition, all but no. 10 received either insulin coma

treatment or electroshock treatment, but the somatic therapy was not necessarily given during the course of this investigation.

The method for estimation of free plasma reducing steroids, based on the reduction of tetrazolium blue, has been recently published.[9] Hydrocortisone-like compounds were determined according to the Porter-Silber reaction, as described by Nelson and Samuels.[10] The extraction, concentration, and purification of the plasma extract and the application of the procedures mentioned to this extract have been discussed elsewhere.[11] The responsiveness of the adrenal gland to ACTH infusion was measured by securing blood for analysis before and at the end of a six hour infusion of 500 ml. of 5 per cent glucose containing 30

TABLE II

*Response of Psychiatric Patients to Corticotropin Infusion**

Patient	No. of ACTH Tests	Total reducing steroids (TBRS),† % increase after ACTH		No. of responses below normal minimum % increase	F-like compounds (PRS),† % increase after ACTH		No. of responses below normal minimum % increase
		Range	Average		Range	Average	
1	5	10.30– 70.90	43.06	4	21.00–237.40	21.00	2
2	4	11.80– 27.30	18.35	4	21.50–107.00	50.55	3
3	9	15.80–111.70	52.57	7	22.70–117.90	73.02	5
4	6	10.50–168.10	58.50	5	40.30–169.20	71.80	5
5	6	6.60– 75.80	43.05	5	10.80– 93.04	50.87	4
6	5	32.30– 88.20	57.90	4	56.40–116.20	87.54	1
7	4	44.44– 92.71	70.64	2	46.90–122.50	96.28	1
8	3	16.70– 85.70	57.83	1	29.70–113.60	79.50	1
9	4	9.50–129.20	59.33	2	15.50–146.90	77.15	2
10	11	30.40–111.70	58.12	8	46.10–168.80	86.95	4
11	6	8.70–148.90	58.57	4	18.90–153.40	88.23	3
12	6	3.40– 60.90	36.85	6	4.90–168.90	61.43	5
13	3	80.00–169.22	103.17	1	62.00–232.60	141.53	1
14	2	55.60– 69.20	62.40	1	55.60– 73.30	64.45	1
15	6	11.40– 65.00	28.74	6	27.40–118.30	53.92	5
16	5	26.80– 70.90	35.22	4	39.70–109.00	64.56	3
Total	85			64			46
Average		3.40–169.22	51.70		4.90–237.40	76.50	
Average of healthy male adults	19	66.22–168.52	115.88	—	69.75–183.98	120.95	—

* 30 I.U. of corticotropin (ACTH) in 500 ml. of 5 per cent dextrose in water infused over a six hour period. Lots of corticotropin used in this study were: control series, P46806C and P46604C; and, patients, P46604C and P46705C.

† TBRS = tetrazolium blue reducing steroids; PRS = phenylhydrazine reacting steroids.

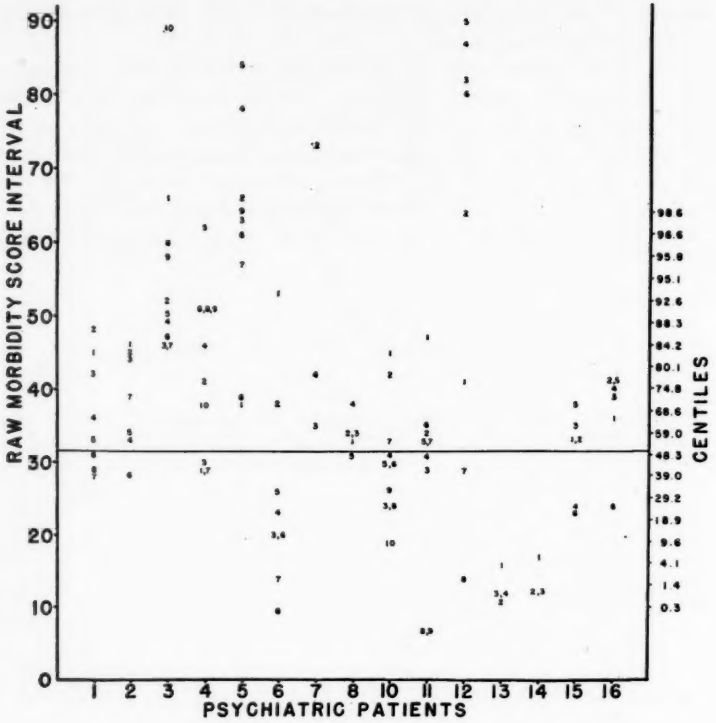

FIG. 1. Psychiatric evaluation of patient's symptomatology. The sequence of ratings are indicated for each patient by numerals located to indicate the raw morbidity score interval for the corresponding rating. Raw morbidity score interval is the difference between the individual patient's raw score and the standard total score. The centile indicates the frequency of the raw score interval as obtained on a "normative population" consisting of 423 hospitalized patients without mental illness whose mean value is indicated by a line.

I.U. of corticotropin (Armour). The lots of corticotropin used are indicated in table II. The fasting samples were all taken at approximately 8 a.m.; then the ACTH infusion was started; next the patient was allowed to eat breakfast and lunch at the regular time. Fasting blood samples were obtained at two week intervals for the first few weeks and approximately every four weeks thereafter. An attempt was made to secure blood for analysis near the time that the psychiatric symptomatology was scored; no more than a 48 hour discrepancy existed in any instance.

The psychiatric symptomatology was recorded by means of a scale known as the Multi-

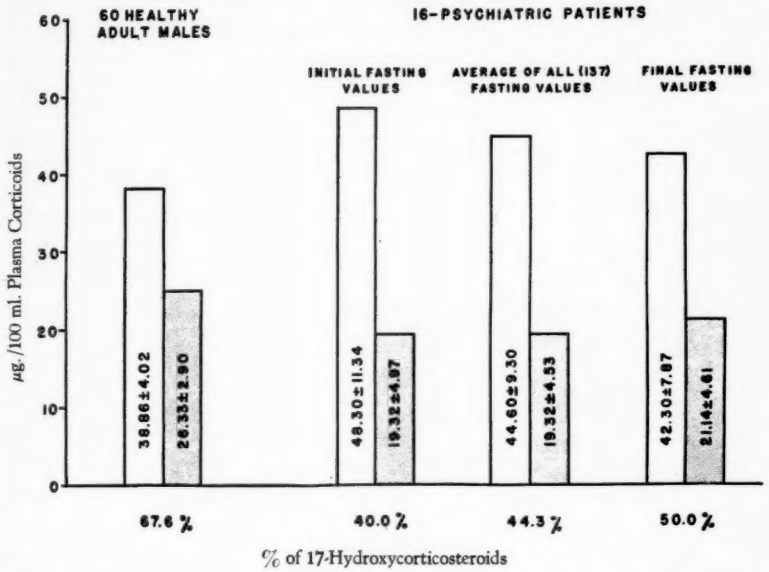

FIG. 2. Average concentration and distribution of plasma corticoids in patients and healthy subjects. Open columns = total reducing corticoids, stippled columns = F-like reducing corticoids. Numbers on each column give average value and standard deviation.

dimensional Scale for Rating Psychiatric Patients, hereafter referred to as the MSRPP.* It "consists of 62 brief unlabeled graphic rating scales presented in a random order. The schedule secures, in a relatively objective and quantitative form, a description of the observable behavior or readily inferable traits and common symptoms of hospitalized patients. The scales represent a broad sample of important symptoms characteristic of the functional psychoses. They demand a minimum of interpretation on the part of the observer, and they yield judgments relatively unbiased by the rater's point of view or theoretical persuasion." The scores for the individual patients at various times are shown in figure 1. Each of 44 items was rated on the basis of 1, 2, 3, 4, and 5, or unratable. The arithmetical values of the items are totaled into factors, and the sum of the factors indicates total morbidity manifested by the patient. These sums may be subtracted from norms so that variants can be established for statistical purposes. It is the belief of the authors that, of the popular scales, this one is the most satisfactory for showing symptoms of psychiatric illness in a quantitative way. The reliability of the rating scale used is naturally of considerable im-

* This scale was devised by Maurice Lorr, Ph.D., Chief of the Neuropsychiatric Research Office, Veterans Administration Regional Office, Washington, D. C. The scale itself is VA Form 10-2488, February, 1954. Description of this scale is shown in Veterans Administration Technical Bulletin TB-10-507, Nov. 16, 1953.

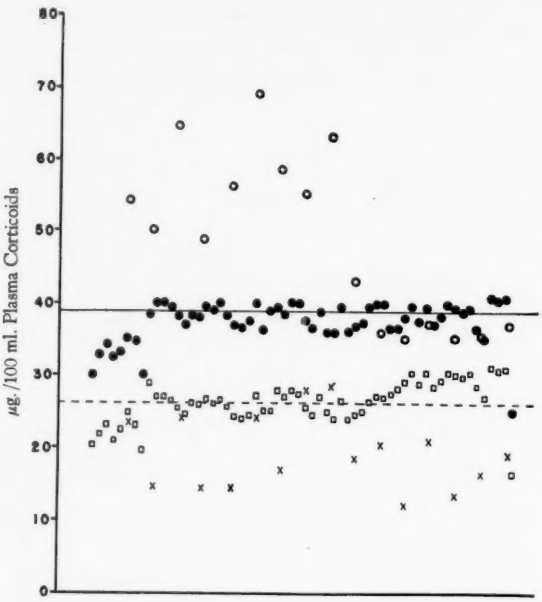

FIG. 3. Distribution of individual values for initial plasma corticoids of patients and healthy subjects. Open circle = total reducing plasma corticoids of patients; closed circle = total reducing plasma corticoids of healthy subjects; cross = concentration of the F-like fraction of plasma corticoids of patients; and the square = the concentration of the F-like fraction of plasma corticoids of healthy subjects.

portance when it is used for correlation with other findings. This scale has been subjected to investigation that has indicated it has a relatively high degree of reliability and that the values assigned to the various items by different raters are consistent about 75 per cent of the time. Moderate deviations between different raters occur with some frequency in the remaining percentage, but gross deviations are uncommon. In the present project all of the ratings, except those on 1 patient, were made by the same rater, an experienced physician. The normative values for this scale were derived from evaluation of 423 hospitalized patients.

RESULTS AND COMMENTS

Table I and figure 1 summarize pertinent clinical information concerning the individual patients included in this study. Determination of the concentration of total free plasma corticoids (TBRS) and hydrocortisone-like compounds (PRS) includes values obtained on 60 healthy laboratory workers, residents, and amputees. The range of concentration, standard deviation, average values, and percentage of total corticoids reacting like hydrocortisone for both patient and healthy subjects are shown in figure 2. The patient data presented in figure 2 include the averages of the initial and final plasma values obtained during this study, as well as an average of all the fasting values obtained on the psychiatric patients. These results demonstrate that the patients averaged higher total reducing corticoids and a lower proportion of F-like compounds in the circulation than had the

healthy subjects. In figure 3, the distribution of the initial individual values of the patients and of the healthy subjects is shown as a scattergram.

Comparison of the initial values obtained on the patients with those for the healthy subjects indicates that slightly over half of the patients' values for total reducing steroids exceeds the upper limits of the values obtained on healthy subjects. The values obtained on all of the mentally ill patients throughout the study are summarized in table III. Slightly less than half (61) of all the fasting values for the TBRS fraction was above the upper limits of the normal range, and a somewhat smaller number (50) of the PRS values fell below the lower limits of the range obtained on the healthy subjects. The percentage of the total circulating free reducing corticoids made up of PRS-reacting substances was consistently less (133 times out of 137 chances) in the patients than in the healthy subjects.

The diurnal variation in plasma corticoid concentrations was determined in 6 of the

TABLE III

Average of All Fasting Plasma Corticoid Values on Patients

		Total reducing steroids (TBRS)*		F-like compounds (PRS)*		% as F-like compounds	
Patient	No. of determinations	Average μg./100 ml.	No. of values above 45 μg./100 ml.†	Average μg./100 ml.	No. of values below 16.5 μg./100 ml.†	Average %	No. of values below 60%
1	9	53.91 ± 7.93	8	16.34 ± 3.62	5	30.30	9
2	9	45.65 ± 13.37	4	21.47 ± 5.66	3	47.03	8
3	15	43.12 ± 8.94	5	18.26 ± 4.67	6	42.34	15
4	11	43.74 ± 5.74	3	18.85 ± 2.20	1	43.09	11
5	10	40.69 ± 8.57	3	18.97 ± 6.40	4	46.62	9
6	11	38.28 ± 8.44	3	19.41 ± 6.70	5	50.70	9
7	6	33.85 ± 10.04	0	14.28 ± 3.57	4	42.18	6
8	5	38.36 ± 5.40	1	17.10 ± 6.11	2	44.57	5
9	6	46.26 ± 12.76	4	19.92 ± 5.55	2	43.06	6
10	13	50.44 ± 11.56	9	20.22 ± 4.66	5	40.08	13
11	8	40.09 ± 8.53	2	12.40 ± 4.31	7	30.93	8
12	9	49.89 ± 10.77	7	21.15 ± 3.31	2	42.39	9
13	5	43.69 ± 5.68	2	21.24 ± 2.79	0	48.61	5
14	3	50.00 ± 5.83	2	26.27 ± 1.22	0	52.54	3
15	9	48.82 ± 11.57	5	22.18 ± 4.89	2	45.43	9
16	8	46.75 ± 13.71	3	21.13 ± 6.81	2	45.19	8
Total	137		61		50		133
Average		44.60 ± 9.30		19.32 ± 4.53		43.44	

* Tetrazolium blue reducing steroids (TBRS) and phenylhydrazine reacting steroids (PRS) are both expressed as the microgram equivalent of compound F (hydrocortisone)/100 ml. of plasma.

† 45 μg./100 ml. is the upper limit of the normal range for TBRS values, and 16.5 μg./100 ml. is the lower limit of the normal range for PRS values on 60 healthy male subjects.

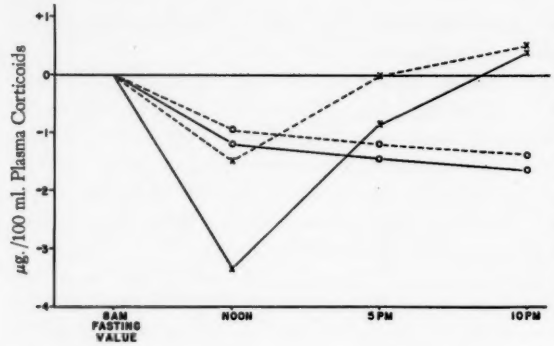

FIG. 4. Diurnal variation in the plasma concentration of corticoids in 6 patients (no. 1–6) with acute mental illness and in 6 healthy medical residents engaged in routine duties. Solid line = variation in plasma concentration of total plasma reducing corticoids as compared to value at 8 a.m.; broken line = variation in plasma concentration of F-like compounds as compared to 8 a.m. value. Open circle = healthy subjects; cross = mental patients.

patients with mental illness. These results and similar observations made on 6 healthy subjects are shown in figure 4. The increased plasma values obtained on the 5 p.m. and 10 p.m. samples from the psychotic subjects were consistent throughout the group and constituted a qualitative difference from the diurnal fluctuations obtained on the healthy subjects. Both TBRS and PRS fractions qualitatively behaved similarly in the patients, but the magnitude of daily fluctuations of the TBRS fraction was relatively greater. Evidence of a disturbed diurnal rhythm of adrenal steroid secretion was likewise obtained by Reiss et al[6] in their studies on urinary steroids in psychiatric patients.

Healthy subjects infused with 30 I.U. of corticotropin over a six hour period have approximately double the initial concentration of corticoids by the end of the infusion (table II). Infusion of the psychiatric patient with corticotropin usually resulted in a smaller increase in plasma corticoids than occurred in the healthy subjects (fig. 5 and table III). In a few instances there was essentially no response to the infusion and some patients gave a widely varying response to corticotropin infusion. Considerable variation was observed in the response of healthy subjects, although their percentage increase over the fasting value was in general of greater magnitude and less variable as compared to one another than the patients' response. The hydrocortisone-like compounds in the circulation usually increased relatively more than the TBRS fraction in response to corticotropin infusion in the patient than in the normal group.

Pincus et al[5] report that ACTH injection failed to cause a normal increase in the 17-ketosteroid excretion of patients with schizophrenia, although the initial rate of excretion was somewhat higher than that of the control subjects. Reiss et al[8] found that the percentage of patients giving a complete positive response to ACTH, as judged by eosinophiles, urinary ketosteroids, and uric acid excretion, was 31 per cent for chronic schizophrenia, while in acute schizophrenia a complete response was obtained in 54 per cent of the patients. The subjects included in the present study are more nearly comparable to the last mentioned group. The many research findings quoted by Altschule suggest that the adrenal cortices are hyperactive during the early part of a severe psychiatric illness and that later on their activity decreases to normal.[18] The plasma steroid response to ACTH infusion reported

here largely demonstrates a hyporeactivity of the adrenal cortex to this type of stimulation. It is also desirable to determine the response to different amounts of ACTH, to determine the amount required to give a response comparable to that obtained in healthy subjects.

Observations were made on the elevation of the plasma corticoid values following oral ingestion of 100 mg. of cortisone acetate by 15 of the patients included in this study. The extent and duration of elevation of the plasma corticoid values as compared to the response of a group of healthy subjects is shown in figure 6. The maximum elevation observed one hour after cortisone ingestion for 11 of the patients was less than the response of healthy subjects; 3 had a normal response and 1 patient had a high response. The magnitude of the plasma response to ingested cortisone appeared to be independent of the initial fasting value. Both the patient and healthy groups had essentially returned to their initial values four hours after ingestion of cortisone. The flatter "tolerance" curves obtained on the patients could be due to a reduced rate of absorption or increased rate of removal from the circulation. The same test performed on a few patients with elevated fasting plasma corti-

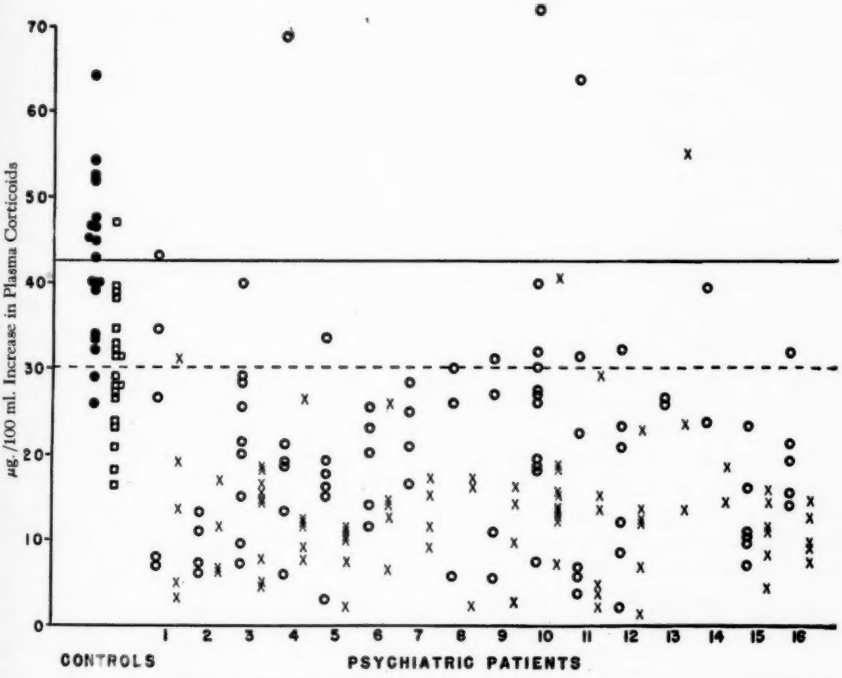

FIG. 5. Scattergram showing increase in plasma corticoids in response to ACTH infusion in individual patients with mental illness and in healthy subjects. Solid circle = total reducing corticoid increase in healthy subjects; open circle = total reducing corticoid increase in patients; square = increase in F-like fraction of healthy subjects; and, cross = increase in F-like fraction of patients.

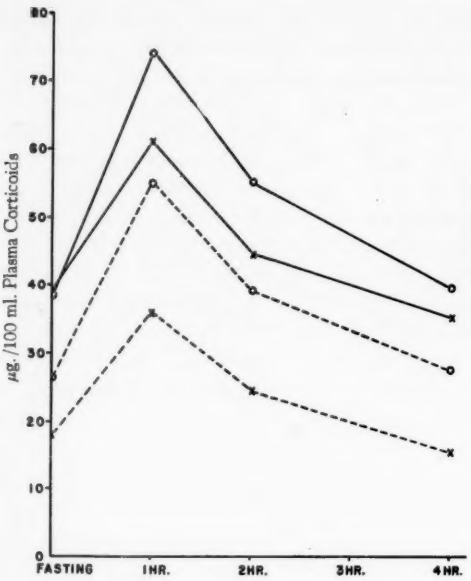

FIG. 6. Average plasma corticoid response to ingestion of 100 mg. of cortisone acetate by fasting healthy subjects and patients with mental illness. Solid line = total plasma reducing steroids; broken line = F-like plasma reducing steroids. Open circle = 12 healthy subjects, cross = 15 patients with mental illness.

coids associated with chronic hyperfunction of the adrenal cortex (Cushing's syndrome) has given a more sustained elevation of the plasma corticoids as compared to healthy subjects.[20]

Compounds A and B are reported to be present to some extent in the circulation. Sweat[21] found that approximately one third of the corticoids in the peripheral blood of healthy subjects appeared in the corticosterone region of the chromatogram. According to Morris and Williams,[12] next to compound F, corticosterone (compound B) is present in normal plasma in the largest amounts. This compound does react with the TBRS reagent but would not be included in the PRS determination. Compound A or B or other reducing steroids lacking a 17-hydroxy group may be responsible for the increased TBRS values observed in these patients. Evidence exists that the proportion of steroids secreted by the adrenal may change,[13] although Bush[14] reported that the proportions of cortisone and hydrocortisone are constant during acute stimulation with ACTH; Kass et al[15] found that prolonged adrenal stimulation with ACTH in the rabbit increased the proportion of hydrocortisone produced by the stimulated gland. The possibility must not be overlooked that the additional tetrazolium-reacting material is extra-adrenal in origin. Against this is the fact that the low ratio of total to F-like fraction is also reflected in the increased corticoid concentration resulting from ACTH infusion in patients with an initially low ratio.

Whether the increased total plasma values are due to increased liberation of steroids into the circulation or to a decreased rate of utilization has not been established. The increased plasma concentration of circulating reducing corticoids in subjects with a reduced response

of the adrenal gland to ACTH stimulation appears paradoxical. By themselves these results would suggest that there must be a reduced rate of corticoid excretion or utilization by the tissues, but, if the response to cortisone ingestion is also considered, this explanation of the elevated values appears to be unlikely. Assuming that all the reducing steroids measured are adrenal in origin, one must conclude that the pattern of corticoid elaboration or relative rates of removal is altered from the normal. It should be pointed out that the present method of analysis only provides data regarding the concentration of plasma corticoids not conjugated with glucuronic acid or present in some other form that prevents the extraction by chloroform-like solvents. Bongiovanni et al[16] have shown that a considerable portion of plasma corticoids are in a conjugated form. It may be that the extent of corticoid conjugation is altered from normal in the patient with psychiatric illness.

A reduced percentage of PRS-reacting substances has been found to occur in certain other disease states, both endocrine and nonendocrine in origin,[11] but it usually is accompanied by a decrease in the total reducing steroids. Observations on 3 patients with adrenal adenoma or bilateral hyperplasia associated with manifestations of Cushing's disease have shown both the total and hydrocortisone-like fractions to be similarly increased so that the percentage of hydrocortisone in the circulation remained within normal limits.[20]

Muscular inactivity and emotional tension may contribute to the elevation of urinary ketosteroids, according to the observation reported by Holmes and Ripley on a single patient.[17] Rhythmic fluctuations in the amount and proportions of urinary 17-ketosteroids excreted by a patient with manic-depressive psychosis were clearly demonstrated by the analyses reported by Reiss et al.[6] However, it cannot be assumed that any parallelism need exist between the concentration of plasma corticoids and the urinary values for the neutral 17-ketosteroids. Numerous instances of dissociation between the values reflecting these two aspects of adrenal function have been encountered.

Presumably, the altered responsiveness of the adrenal gland and abnormal distribution and concentration of plasma corticoids are related to the disturbed emotional state of the patient. The adrenal would be judged hyperfunctional on the basis of an increase in total reducing steroids and normal or hypofunctional in most instances as judged by the concentration of hydrocortisone in the plasma. The ACTH response also indicates a hypofunctional state of the adrenal glands of the patients.

Attempts to relate the plasma corticoid values to the psychiatric evaluation of the patient's state have on the whole been unsuccessful. The fact that psychiatric patients present biochemical abnormalities suggests that it may be possible to make meaningful correlations with the psychiatric findings. However, a gross correlation such as was attempted in the present study may have overlooked variables of crucial importance. More detailed observations concerning the emotional conflicts and defense mechanisms may furnish a more satisfactory basis for determining whether correlations between the plasma corticoids and psychiatric conditions are possible.

SUMMARY

Sixteen patients with acute mental illness, mostly schizophrenia, frequently had an

increased plasma concentration of total free plasma reducing steroids, while the hydrocortisone-like compounds of plasma usually fell in the lower range or below the normal concentration. The proportion of plasma corticoids made up of hydrocortisone was consistently less than normal in this group. The plasma corticoid response to ACTH infusion was less than that observed in healthy subjects. The plasma corticoid elevation in response to cortisone ingestion was less than normal in 11 of 15 patients tested. The diurnal variation in the concentration of plasma corticoids differed in the patient and control groups. Plasma corticoid data obtained on these patients provide direct evidence of altered adrenocortical function in patients with acute mental illness. No positive correlation could be made between plasma corticoids and emotional disturbances, using the Multidimensional Scale for Rating Psychiatric Patients.

RESUMEN

Dieciséis pacientes con enfermedades mentales agudas, la mayoría esquizofrénicos, presentaban con mucha frecuencia una concentración hemática elevada de esteroides reductores del plasma libre total, mientras que los compuestos similares a la hidrocortisona hemática estaban por debajo del promedio normal o de la concentración normal. La proporción de los corticoides hemáticos procedentes de la hidrocortisona fue uniformemente menor de lo normal en los individuos sanos. La elevación de los corticoides hemáticos como respuesta a la ingestión de cortisona fue menor que lo normal en 11 de 15 pacientes con quienes se experimentó. El cambio diurno de la concentración de corticoides fue distinto tanto en los pacientes como en los grupos testigo. Los datos sobre los corticoides hemáticos obtenidos en estos pacientes proporcionan una prueba directa de la alteración de la función corticosuprarrenal en pacientes con enfermedades mentales agudas. No se pudo establecer ninguna relación positiva entre los corticoides hemáticos y los trastornos emotivos, por medio de la Escala Multidimensional para clasificar pacientes psiquiátricos.

RESUME

Seize malades atteints de maladie mentale aiguë, pour la plupart schizophrènes, ont fréquemment présenté une augmentation de la concentration plasmatique de stéroïdes réducteurs de plasma totaux, pendant que les composés plasmatiques du type hydrocortisone généralement tombaient à un niveau plus bas ou au-dessous de la concentration normale. La proportion de corticoïdes plasmatiques composés d'hydrocortisone était constamment moindre que la normale dans ce groupe. La réponse corticoïde plasmatique à une infusion d'adrénocorticotrophine fut moindre que celle observée chez les sujets en bonne santé. L'élévation corticoïde plasmatique en réponse à l'ingestion de cortisone fut moindre que normale chez 11 des 15 malades testés. La variation quotidienne dans la concentration des corticoïdes plasmatiques différait chez le malades et les groupes témoins. Les données en corticoïdes plasmatiques obtenues chez ces malades fournissent des preuves directes de la fonction adrénocorticale modifiée chez les malades avec maladie mentale aiguë. On n'a pas pu trouver de corrélation positive entre les corticoïdes plasmatiques et les troubles émotifs en employant la "Multidimensional Scale" pour évaluer les malades psychiatriques.

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17-Hydroxycorticosteroid Levels in the Peripheral Blood of Schizophrenic Patients

A Preliminary Study

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Despite the recent widespread interest in the possible implication of the adrenal-pituitary axis in the psychotic process, there have been relatively few definitive studies on the levels of 17-hydroxycorticosteroids (17, 21-dihydroxy-20-ketosteroids), hereafter written 17-OHCS, in the peripheral blood of psychotic patients. Two reports in the literature are worthy of mention: that of Bliss and his associates,[1] in connection with a study of the influence of electroconvulsive therapy and of insulin coma, and that of Dohan et al[2] on levels during insulin shock therapy. The present study is an outgrowth of work initiated by the Sacklers[3] in this laboratory on the possible significance of the adrenal cortex in mental disease.

MATERIALS AND METHODS

The study was performed on two groups of psychotic subjects: 21 "agitated" and 21 "deteriorated" hospitalized male psychotics, all residing in the same pavilion on the Continued Treatment Service. A group of 19 male staff members of the Institute and Hospital and 7 donors to the blood bank of the Queens General Hospital served as normal controls. The ages in this "normal" group ranged from 26 to 55 years. None of the subjects had taken any drug in the week prior to blood withdrawal, nor had any of the patients been given electric shock or insulin therapy in that time. Blood samples of 20 ml. volume were taken during the postabsorptive period from 9:30 to 10:30 a.m., drawn from the antecubital vein in a syringe rinsed with a 1 per cent solution of heparin, and were transferred into a dry centrifuge tube. After centrifugation, the plasma was separated and the 17-OHCS was determined in the plasma according to the method of Porter and Silber.[4]

RESULTS AND COMMENTS

In our experimental design we planned to use the Porter-Silber method as a screening procedure and to resort to the more specific, but more laborious, method of Nelson and Samuels[5] if abnormally high values were found. In view of the comparatively normal values obtained in our study it was unnecessary in this work to make use of the latter method.

The values are presented in tables I, II, and III, together with some characteristics of clinical status of the patients. The mean for the normal group (table I) is 18.23, with a range of from 3 to 34 gamma/100 ml. For the agitated group (table II) the corresponding

value is 17.62, with a range of from 0 to 49 gamma/100 ml., and for the deteriorated group (table III) it is 16.71, with a range of from 0 to 41 gamma/100 ml. If from 10 to 25 gamma/100 ml. is taken as the normal range, 3 in our control series exceed the upper limit and 3 fall below the lower limit. In the agitated group 2 exceed the range and 5 fall below; in the deteriorated group 6 are over the limit and 6 below.

These figures may also be compared with the values available in the literature. The mean values for 120 normal adults in 267 determinations were reported by Bliss et al[6] in 1953 to be 13 gamma/100 ml., with a range of from 2 to 34 gamma/100 ml. The mean for 91 normal males in 195 determinations in this series was 12 gamma/100 ml. In a study on the effects of ACTH on the blood level of this steroid, Bliss et al[7] reported 82 control values averaging 16.84 in a series of patients with mixed diagnoses.

In psychotic patients the control values reported by Bliss et al[1] in their study on the

TABLE I

Plasma 17-OHCS in 26 Normal Subjects

Subject	17-OHCS, gamma/100 ml.
C1	15
C2	18
G	7
O	20
H	29
R	27
F	11
S	4
V1	20
C3	18
W1	3
B	21
S3	34
W2	15
W3	22
T	32
V2	17
L.D.	17
T.D.	13
G.C.	19
T.M.	16
K.B.	23
J.R.	10
F.B.	25
E.L.	15
J.P.	17

Number = 26, mean = 18.23, sigma = 8.95.

TABLE II

Plasma 17-OHCS in 21 Agitated Psychotic Patients

Subject	Age, yr.	Diagnosis	Psychiatric status	17-OHCS, gamma/100 ml.
MV	38	D.P., paranoid	Excitement, overactivity	18
MW	31	D.P., paranoid	Violently assaultive, angry speech	22
CL	48	D.P., hebephrenic	Overactive, assaultive, sits rigid, destructive to clothing	21
OT	26	D.P., catatonic	Overactive, assaultive, paranoid ideas, hallucinations	19
NM	26	D.P., catatonic	Overactive, antagonistic, excited, noisy, aggressive behavior	25
GW	30	D.P., catatonic	Overactive, assaultive, paranoid ideas, auditory hallucinations	7
CF	19	D.P., catatonic	Assaultive without provocation, homicidal, requiring restraint	18
CA	44	D.P., catatonic	Poor contact, delusional, hostile, assaultive, auditory hallucinations	17
PJ	21	D.P., catatonic	Antagonistic, actively suicidal, requiring restraint	24
MC	33	D.P., catatonic	Seclusive, overactive, constantly racing about, poor contact, hallucinating	23
DE	31	D.P., catatonic	Seclusive, negativistic, paranoid, threatening	11
VA	27	D.P., catatonic	Seclusive, negativistic, at times assaultive without provocation, delusional	7
FR	25	D.P., catatonic	Restless, constantly pacing, inaccessible	5
WR	50	D.P., catatonic	Actively hallucinating, paranoid at times, incontinent	14
FR	26	D.P., catatonic	Overactive, shouting all day, requiring restraint, out of contact, hallucinating	49
MI	36	D.P., catatonic	Assaultive, shouting all day, requiring sedative and sheet restraint	12
HH	43	D.P., hebephrenic	Agitated, overactive, assaultive, requiring constant restraint	19
BB	55	D.P., paranoid	Overactive, noisy, seclusive, hallucinatory	—
AM	60	D.P., hebephrenic	Assaultive, incontinent, destructive, out of contact	36
CF	45	D.P., catatonic	Overactive, pacing aimlessly, throws furniture, wets and soils, constantly pushes other patients, disconnected speech, hallucinations	23
OJ	31	D.P., paranoid	Agitated, uncooperative, untidy	—

D.P. = dementia praecox. Number = 21, mean = 17.62, sigma = 12.07.

TABLE III

Plasma 17-OHCS in 21 Deteriorated Psychotic Patients

Subject	Age	Diagnosis	Psychiatric status	17-OHCS, gamma/100 ml.
NJ	29	D.P., catatonic	Up and about, confused, idle, untidy, disinterested, requires spoon feeding, wets, soils, speech irrelevant and infrequent, inaccessible	—
OB	37	D.P., paranoid	Up and about, idle, untidy, emotionally flattened, poor contact, inaccessible	20
KA	46	D.P., hebephrenic	Quiet, seclusive, disinterested, poor contact, mumbling, hallucinates, no insight	—
FD	45	D.P., simple	Up and about, stands idly in one spot, completely mute and regressed, untidy, no contact	28
BJ	31	D.P., catatonic	Up and about, untidy, confused, seclusive, eats poorly, at times assaultive, poor contact	14
DW	46	D.P., paranoid	Up and about, quiet, perplexed, emotionally blunted, occasionally laughs to himself, out of contact	15
AA	48	D.P., catatonic	Up and about, idle, disinterested, occasional urinary incontinence, regressed and indifferent, completely out of contact	27
MD	46	D.P., hebephrenic	Auditory hallucinations, regressed, withdrawn, recent and remote memory defects	24
HW	42	D.P., catatonic	Regressed, inaccessible, untidy, wets and soils, auditory hallucinations	41
FS	29	D.P., catatonic	Up and about, wanders aimlessly, untidy, seclusive, silly, inappropriate, speech disconnected and incoherent, inaccessible	32
BW	32	D.P., paranoid	Up and about, idle, self-absorbed, bewildered, laughing to self, mumbling prayers to himself	15
GP	21	D.P., undifferentiated	Up and about, self-absorbed, confused, disconnected and hesitant speech, auditory hallucinations, poor contact	21
BA	36	D.P., paranoid	Up and about, untidy, seclusive, idle, withdrawn, bizarre religious delusions, auditory hallucinations, on interview mute for long time, then rambles disconnectedly	14
FC	36	D.P., catatonic	Up and about, disinterested, emotionally blunted	—
FJ	27	D.P., hebephrenic	Quiet, withdrawn, immobile, fixed stare, psychomotor retardation, completely inaccessible	7
CW	49	D.P., paranoid	Up and about, assaultive without provocation, disconnected and incoherent speech, emotionally elated, regressed, auditory hallucinations, memory defects in both fields, insight lacking	26
GD	45	D.P., hebephrenic	Up and about, idle, seclusive, detached, disinterested in his personal injuries, silly, inappropriate, regressed, constantly grimacing, cannot sit still, laughing for no obvious reason, speech incoherent and disconnected, auditory hallucinations	11

Table III continued on page 280

TABLE III (*Continued*)
Plasma 17-OHCS in 21 Deteriorated Psychotic Patients

Subject	Age	Diagnosis	Psychiatric status	17-OHCS, gamma/100 ml.
GJ	28	D.P., catatonic	Overactive, negativistic, will not tolerate clothes, has to be dragged to dining room, will not eat own food but steals others', grimaces, incoherent	4
RW	42	D.P., hebephrenic	Seclusive, assaultive without provocation, eats clothing, eats and sleeps poorly, wets and soils, out of contact, mute, inaccessible	29
WJ	19	D.P., catatonic	Quiet, self-absorbed, idle, mumbling, inaccessible	7
PH	46	D.P., hebephrenic	Mute, incooperative, agitated, annoying others constantly, angry at times, laughing foolishly occasionally, wets, does not follow simple commands, constantly feeling any accessible object in environment	16

D.P. = dementia praecox. Number = 21, mean = 16.71, sigma = 11.17.

effect of electroconvulsive and insulin coma therapy may be used for comparison with our study. Since all our subjects were males, the values for the 16 schizophrenic males presented in the Bliss report are assembled in table IV. The mean is 19.38, with a range of 11 to 35, and with three values over 25 and none under 10.

TABLE IV
Control Plasma 17-OHCS in 16 Psychotic Patients
(Compiled from Bliss et al[6])

Subject	17-OHCS, gamma/100 ml.
C	35
C2	26
C	16
C	18
H.C.	23
H.C.	22
H.C.	16
H.C.	15
H	18
VB	11
T	14
T	28
B	20
S	19
S	18
W	11

Number = 16, mean = 19.38, sigma = 8.05.

TABLE V
Distribution of 17-OHCS Values

Groups	No. of subjects	Mean values of 17-OHCS, gamma/100 ml.	Sigma	Values under 10 gamma/100 ml.		Values between 10–25 gamma/100 ml. (normal)		Values over 25 gamma/100 ml.	
				No.	%	No.	%	No.	%
Normal control	26	18.23	8.95	3	12	20	77	3	12
Agitated schizophrenic	21	17.62	12.07	5	24	14	71	2	10
Deteriorated schizophrenic	21	16.71	11.17	6	29	9	43	6	29

In table V the distribution of values into normal, above normal, and below normal in the present series is set forth. The deteriorated group seems to have a greater tendency to below- and above-normal values than the normal group, although this tendency is not statistically significant, p being only .06. The agitated group shows a similar tendency, although a larger number of values will have to be obtained to determine statistical significance.

This comparative study indicates that the levels of 17-OHCS in the peripheral circulation of agitated and deteriorated schizophrenic patients do not differ significantly from each other or from normals; it is clinically recognized that agitation and deterioration may be phases of the same disorder. There is, however, a tendency of the agitated and deteriorated groups to show more individuals with abnormally high or abnormally low values.

SUMMARY AND CONCLUSIONS

The plasma level of the 17-hydroxycorticosteroids in the peripheral circulation of 21 agitated and 21 deteriorated schizophrenic patients was determined by the Porter-Silber method. The mean values of the psychotic groups do not differ significantly from each other or from a normal population. There is a tendency of the psychotic groups to show more individuals with abnormally high and abnormally low values.

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RESUMEN

Se ha determinado por el método Porter-Silber, la concentración hemática de los 17-hi-

droxicorticosteroides en la circulación periférica de 21 pacientes esquizofrénicos agitados y 21 deteriorados. Las concentraciones de los grupos psicóticos no difieren significativamente entre sí ni son distintas a las de la población normal. Existe una tendencia de los grupos psicóticos a mostrar más individuos con valores anormalmente altos y anormalmente bajos.

RESUME

Le taux plasmatiques des 17-hydroxycorticostéroïdes dans la circulation périphérique de 42 schizophrènes, dont 21 agités et 21 détériorés, a été déterminé par la méthode de Porter-Silber. Les taux des groupes psychotiques ne diffèrent pas grandement l'un de l'autre ou même du sujet normal. Il y a tendance dans les groupes psychotiques d'y avoir plus d'individus présentant des taux soit anormalement élevés, soit anormalement bas.

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Anxiety States in the Army Associated with Overactivity of the Thyroid

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The acute psychiatric Army case seems to be particularly suitable for psychoendocrine investigation, not because there is anything special in the symptoms encountered, but because in the Army similar stresses affect large numbers of servicemen in a relatively similar environment. From an etiologic point of view, the chief environmental influence is the Army life with its demands of discipline and training. This offers an opportunity to study, under similar conditions, endocrine adaptation in association with psychiatric changes in response to various precipitating causes in different personality types.

It has been shown[11, 12] that the same psychiatric symptom can be connected with different endocrine deviations and that, on the other hand, the same endocrine deviation can be associated with different psychiatric disturbances.

At present it is possible to progress only by means of longitudinal investigations on individual patients, correlating the endocrine and psychiatric changes observed. Where deviations from the normal endocrine pattern are found, it is now possible, with recent improvements in the methods of investigation and in the production of hormones, to normalize in some patients the endocrine disturbance and to study the effect of such change in the mental reaction of the patient.

This paper describes some psychiatric syndromes in which there were found concomitant endocrine disturbances and for which the appropriate hormone therapy was given and the effects on clinical progress studied in each case. The clinical changes were coordinated with the biochemical findings. In this respect, advantage is being taken of the relatively uniform Army situation for the purposes of these investigations. This uniformity cannot be readily obtained in civil practice because of the great variation of the environment.

One of the concomitant endocrine disturbances worthy of special mention but rarely encountered in clinical routine endocrinology, though not infrequently seen in psychiatric illness, is that of insensitivity of the body periphery to a particular hormone, the production of which is in or above the normal range. For instance, a relative insensitivity to thyroid hormone can occur when, although the thyroid activity as measured by the I^{131} tracer method is normal, or although the quantities of the hormone produced are even above the

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normal range, yet the basal metabolic rate is below the normal range[13] and the skin is dry and cold. This has already been described by Langfeldt[8] and Hoskins and Sleeper,[7] who found that patients in this state do not react with an increase in the basal metabolic rate even after treatment with high doses of thyroid hormone. There are other patients who, in spite of having normally developed gonads and an androgen excretion rate in or above the normal range, do not show any traces of a beard, while other secondary male sex characteristics either are not fully developed or are abnormal in some way, e.g., hair growth or distribution.

METHODS

Endocrinological Investigations. Every patient was thoroughly investigated clinically, and in none were gross clinically recognizable endocrine deviations found.

For several reasons, the scope of the investigations is at present rather restricted. It is inadvisable to subject certain patients to lengthy examinations and tests, owing to their psychiatric disturbance, while an unnecessarily prolonged period in the hospital renders it more difficult to return the patient to duty. Furthermore, the capacity of any endocrinological laboratory is at present limited as far as exact investigation methods are concerned.

We therefore restricted our investigations mainly to some essential data concerning the thyroid and the adrenal cortex.

Investigations of thyroid activity were carried out by the radioactive tracer method already described.[4] The normal range used for comparison was the same width of normal range as was found in previous investigations. The definition of the normal range is being further improved by the investigation of normal Army personnel serving in this hospital living under the same climatic, nutritional, and environmental conditions as the psychiatric patient.

The parameters previously described[4] illustrate the standards with which the numerical values found in the cases outlined below can be compared. These are as follows: K, the uptake slope of I^{131} during the first hour (increased value >3). R_c, I^{131} uptake by the thyroid in 24 hours in per cent of the injected dose (normal range 25 to 50 per cent). I_t, the thyroid index (ratio between R_c and K) (normal range 1.7 to 7.1).

It has been shown previously[4, 13] that the normal range of thyroid activity, as determined with this tracer method, is in more than 90 per cent of cases in agreement with the generally accepted normal range of the basal metabolic rate. In most cases, clear-cut under- and overactivity of the thyroid as assessed with the tracer method is in agreement with decreased and increased basal metabolic rate values, respectively. In a small number of cases where there was found to be no agreement between the value for the thyroid activity as determined by the tracer method and the basal metabolic rate (as already described above), undersensitivity of the body to thyroid hormone was assumed.

The great advantage of the radioactive tracer method over the basal metabolic rate determination lies in its suitability to detect borderline disturbances of thyroid function. At present, this is the most useful method for detecting early thyroid disturbance. This seems important if one considers the various psychiatric phenomena that frequently occur

in early stages of hypothyroidism[10] but that are only rarely correlated with thyroid disturbance.[12]

It must, however, be recognized that contrary to the basal metabolic rate determination, the radioactive tracer method cannot be repeated at intervals of less than three weeks. In using 25μc. of I^{131}, as was done in these investigations, results in shorter time intervals are invalidated by I^{131} traces remaining in the thyroid from the previous determination.

The total 17-ketosteroids excreted in 24 hours was determined according to the method of Callow et al, 1939. The percentage of different 17-ketosteroid fractions in the total ketosteroids excreted was determined by a chromatographic absorption method on alumina (modification of the method of Dingemanse et al[2]).

The Psychiatric Assessment. The cases were clinically assessed at regular intervals by at least two psychiatrists independently. The changes seen are for the purpose of psychoendocrine correlation recorded in connection with the diagrams of the endocrine changes.

Only patients admitted to the hospital with psychiatric symptoms and signs are considered in this paper. Those suffering from any physical disease that might have complicated the picture were excluded.

It should be stressed that in all cases very careful attention was paid to psychotherapy and occupational therapy, hospital care, and dietary. These in themselves failed to produce any progressive improvement, but because of the various internal and external factors that can contribute to breakdown, it is considered that full use must continue to be made of all these accepted methods.

CASE HISTORIES

Case 1. Acute Anxiety State in a Basically Emotionally Immature Personality. A fair, pallid youth, aged 18 years, in the National Service, was admitted to the Royal Victoria Hospital on Aug. 17, 1954. He complained that he often felt nervous, was scared of the dark, had a sinking feeling in his stomach, diarrhea, and sweating, did not think he would settle down to Army life as he felt different from others, and disliked being away from home. He stated he could not "say things properly" and that he found difficulty in "picking things up," could not mix with the other recruits, and wanted to get away by himself.

A poor scholar, he disliked sports at school and was often the "butt" of his fellows. At about the age of 13 years he became a problem for his parents. He was impudent, rude, and at times became violently ill-tempered; he once assaulted his mother. All his family were relieved when he was called to the service. He had had three progressively better jobs prior to entering the Army. He had never had any interest in girls.

On examination, he was shy, anxious, restless, suspicious, timid, and markedly schizoid. He exhibited marked emotional lability; one moment he was smiling, the next blushing or in tears. His nails were severely bitten. His stream of talk was relevant, rational, logical, and coherent. There was no evidence of disordered thinking, but he spoke slowly. He seemed to have difficulty in understanding simple questions. His thought and mood were congruous, the latter fluctuating rapidly from tears to smiles. He was well orientated in time and place; memory was intact and concentration unimpaired. He was below average intelligence (Matrix S.G. 5). There was no evidence of hallucinations or delusions.

Endocrine Investigation. The initial radioactive iodine thyroid test on this patient gave a 24 hour uptake of 74 per cent of the injected dose, a value usually associated with clinically recognizable hyperthyroidism. Other than a slightly increased pulse rate (108), the patient showed no signs of thyroid overfunction, and the basal metabolic rate was within the normal

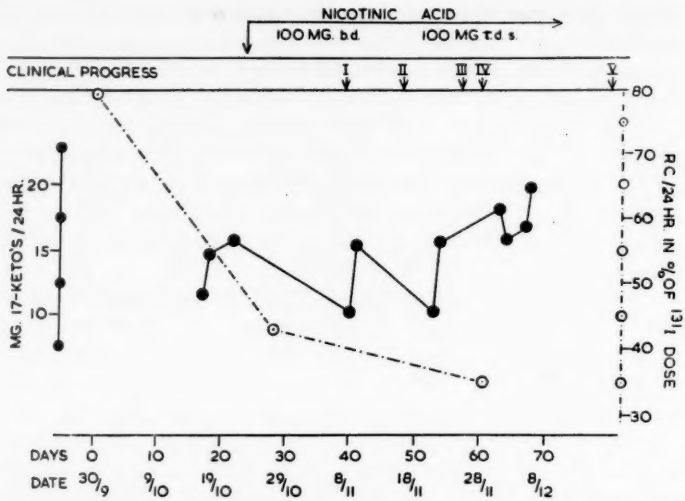

FIG. 1. Clinical progress in case 1. (I) Nov. 7, 1954—Little clinical change. (II) Nov. 16, 1954—Patient shaved for the first time in his life. Acne has appeared on face. Appears more cheerful. (III) Nov. 25, 1954—States he feels more confident in himself but is unwilling to go back into the Army. Basal metabolic rate +8 per cent. Shaved today. Acne present on neck as well as face. (IV) Nov. 28, 1954—Patient looks well. Is happier and exhibits less tension and anxiety, still blushes easily. Shaved again today. Pubic hair distribution definitely male type. Definite clinical improvement. (V) Dec. 18, 1954—Improvement continues. Shaves every second day. (VI) Jan. 7, 1955—Normal hormonal equilibrium. Clinically no psychiatric disability. Discharged.

range (+4). Furthermore, his hands were cold and cyanotic. Although the patient's testicles and penis were of normal size, and the total 17-ketosteroid excretion rate was well within the normal range (13 to 15 mg./24 hours), he showed no signs of beard growth, while his trunk was also free from hair, except for scanty pubic hair with a feminine distribution.

The discrepancy between the tracer and basal metabolic rate results seemed to indicate a state of peripheral undersensitivity to thyroid hormone in this patient, and on this basis, treatment with nicotinic acid was instituted (100 mg. twice a day, increased later to three times a day). The results of the investigations are plotted in figure 1.

The general outline of the changes observed during treatment consisted in some increase of the total 17-ketosteroid excretion rate and a reduction of the high thyroid activity to within a normal range. These changes were accompanied by progressive mental improvement (see figure 1).

The most interesting clinical and endocrine changes observed were the development of acne and the commencement of beard growth after some four weeks of treatment.

Comment. The peripheral undersensitivity in this patient appears to be related to his psychoendocrine disturbance, and clinical improvement is correlated with the administration of nicotinic acid.

Case 2. Subacute Anxiety State with Acute Phobia. The patient, a 44 year old happily married officer, was admitted to the hospital on Nov. 5, 1954, complaining of acute panic attacks, fear of traveling in trains and buses, lack of self-confidence, vague headaches, muscular pains, and fear of fits. His symptoms had been present to a varying degree for about five years until finally he could not do his work and shunned all social contacts. He had had meningitis when 6 years old, which resulted in paralysis of the right upper limb. Since then he had had six typical attacks of jacksonian epilepsy commencing in the right hand. These attacks occurred at irregular intervals; the last three he remembered were in 1938, 1939, and 1947. Since they started he had been on phenobarbitone, 0.5 gr. three times a day, and in addition, since 1947 he had been taking Sodium Amytal, 3 gr. nightly.

On admission the patient was tense, anxious, and very restless. He was emotionally labile, fluctuating

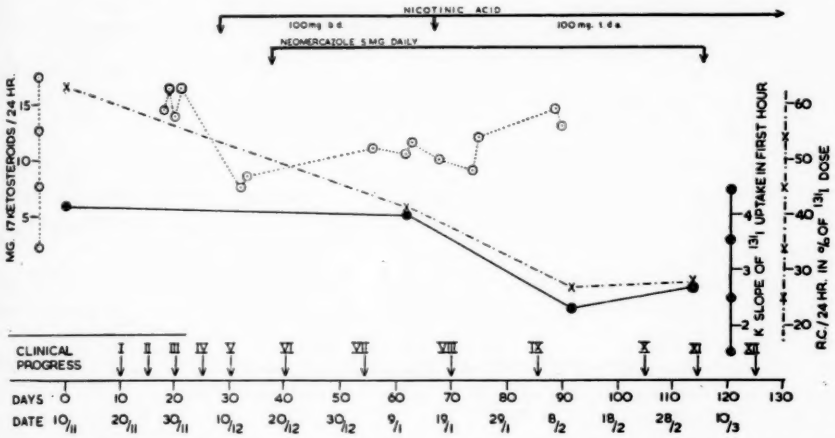

FIG. 2. Clinical progress in case 2. (I) Nov. 20, 1954—Clinical condition unchanged. On being informed that sedatives would be gradually stopped, he became acutely anxious and agitated. Tremor of lips increased. Pulse 80/minute; blood pressure 145/95. (II) Nov. 23, 1954—Electroencephalogram shows a dominant post-central rhythm at 10 cycles/second that is of average voltage and blocks to visual attention. In the resting record, random 6 to 7 cycles/second waves are seen; on overbreathing, this theta becomes more prominent but shows no asymmetry. This is a mildly abnormal record, but there is no positive evidence of any abnormal focus. (III) Nov. 30, 1954—Remains tense, anxious, and agitated. (IV) Dec. 4, 1954—No clinical improvement. (V) Dec. 10, 1954—Feels the effects of vasodilators and complains of tingling sensation in hands and feet. Clinically there is no marked change, but he appears less agitated. However, he complains of fear of venereal disease. Pulse 120/minute. (VI) Dec. 20, 1954—Permitted to go home for Christmas leave, he became agitated and anxious and expressed fear of traveling. Demanded an orderly to accompany him but went on his own. (VII) Jan. 3, 1955—Returned from leave. Alleges severe headaches at home. Relieved to be back but complained of severe panic attack on train. Appears less tense, anxious, and agitated. (VIII) Jan. 19, 1955—Clinically he is improved. Subjectively there is little change—he complains of lack of self-confidence and panic attacks. States that he is rather breathless on exertion. Appears to like discussing and relating his subjective complaints. Pulse 110/minute. (IX) Feb. 4, 1955—Improvement continues. Patient states that he feels much better and sleeps well. Has occasional panic attacks during the day but these are less frequent and not so severe. (X) Feb. 23, 1955—Improvement continues. Panic attacks less frequent and now two to three times a week. (XI) March 8, 1955—Clinical improvement continues. (XII) March 15, 1955—Patient is much happier, sleeps well, and has maintained his clinical improvement. He was discharged fit for duty.

between smiles and tears, and very ashamed of himself for bursting into tears. He complained of lack of self-confidence, pains in the back of the neck, palpitation, and sweating. His sleep was very restless in spite of taking the Sodium Amytal. His hands and feet were cold, his face pale; face and hands were sweating. Pulse rate was 80/minute; blood pressure was 140/90.

The most outstanding deviation observed in this patient was in the activity of the thyroid. He showed a markedly increased thyroid activity as measured by the radioactive iodine tracer method (see figure 2), but the basal metabolic rate was −14.

Because of the state of peripheral undersensitivity, he was treated first with Priscoline, 25 mg. twice a day, but later this was changed to nicotinic acid because he complained of headache with the former. The nicotinic acid appeared to have the effect of unmasking various signs suggesting hyperthyroidism, with tachycardia and palpitations, a resting pulse rate of 120/minute, and further increased tremor and sweating. To counter this, treatment with Neomercazole (No. 2 carbethoxy methimazole), 5 mg. daily, was begun, and this resulted in a gradual decrease in the thyroid activity (fig. 2). This change was accompanied by a corresponding clinical improvement and an alteration in the excretion rate of the total 17-ketosteroids.

This patient's showing on the psychologic test battery demonstrated no change in the basic pattern of his personality, but a great improvement in his condition was inferred from the lowering of defensive mechanisms as shown by the self-rating and by the insight test.

Comment. This patient apparently exhibited a combination of increased thyroid activity and a peripheral undersensitivity to thyroid hormone. The release of the latter resulted in a temporary exacerbation of symptoms and signs of hyperthyroidism, which responded to Neomercazole.

There is evidence from the clinical progress and the biologic findings before and during treatment that there is a relation between the endocrine state and the psychologic disturbances.

In the first few months of treatment the patient required daily supportive psychotherapy and discussions of his problems, in addition to Neomercazole and nicotinic acid.

Case 3. Acute Anxiety State with Phobic Features. A young, unmarried, regular senior noncommissioned officer, aged 24 years, with three years' service, complained of weakness, palpitations, hot and cold feelings, unaccountable panic attacks, and pains in the head. He had lost confidence in his capacity to do his work and felt acutely tense and anxious in the presence of superiors. These symptoms had been present for six months. He was treated in a hospital in Germany with modified insulin for three weeks in December, 1954, and was discharged fit to his unit. Within a week his symptoms returned more acutely than before, necessitating his readmission to the hospital and final transfer to the Royal Victoria Hospital, to which he was admitted on Jan. 19, 1955.

Examination revealed a tidy, neat, clean-shaven, flabby youth with pale face, of high intelligence, who was tense, anxious and agitated, and very restless. He spoke rapidly and precisely but showed no disturbance of thought processes. He exhibited some acne vulgaris on face, neck, and shoulders; there was tremor of the fingers and sweating of the hands and feet. His extremities were cold. Blood pressure was 140/85.

Due to parental friction he had had an unsettled though happy childhood. His sister was in a colony for mental defectives. His maternal grandmother had died in a mental hospital.

Endocrinological Investigations. The most outstanding changes observed in this patient were a total 17-ketosteroid excretion rate above the normal range. The percentage of dehydroandrosterone was very high.

The 24 hour I^{131} uptake of the thyroid of this patient was, at the time of measurement, in the normal range, but the summit of I^{131} uptake was apparently reached some hours

before, as the uptake rate in the first hour (K) was considerably increased, resulting in an I_t above the normal. This permitted the conclusion of an increased I^{131} turnover (see figure 3), which in this case was accompanied by clinical symptoms of sweating, feeling hot, palpitations, and panic attacks.

The endocrine deviation seemed to indicate an overactivity of the pituitary anterior lobe, and on this assumption it was decided to try the effect of treatment aimed at suppressing this activity. Accordingly the patient was given 5 mg. of estradiol benzoate (Dimenformon)

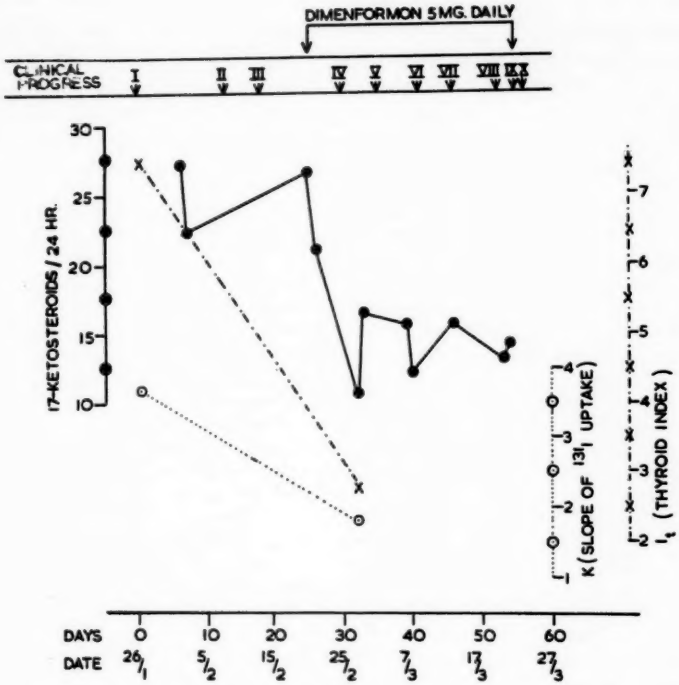

FIG. 3. Clinical progress in case 3. (I) Jan. 26, 1955—Malamud Rating Scale 19. (II) Feb. 8, 1955—Electroencephalogram and roentgenogram of skull reveal no abnormality. Clinical condition remains unchanged. (III) Feb. 13, 1955—Exhibits some obsessional ruminative traits and objectively little improvement. (IV) Feb. 25, 1955—Subjective improvement marked. He states that he feels much happier and contented. Concentration is better. Still sweats on hands and feet. Sleeping well. (V) March 2, 1955—Clinical improvement continues. Is much more cheerful and optimistic. (VI) March 8, 1955—Appears anxious. Feels he is relapsing and had a brief panic attack. Readily accepts that he has not relapsed but that his earlier improvement following injections was more apparent than real. (VII) March 13, 1955—Clinically he is well and cheerful, is contented, keeps himself busy in occupational therapy, and assists in the ward work. (VIII) March 20, 1955—Clinical improvement maintained. (IX) March 22, 1955—Malamud Rating Scale 8. (X) March 23, 1955—Discharged to unit in Category S.7—for review in three months.

daily. Five days after treatment was begun, the thyroid activity and the 17-ketosteroid excretion rate were reduced to normal range. At the same time the patient assured his doctors that subjectively he felt much better. Objectively there was marked clinical improvement, which continued to such a degree that he was sent back to his unit fit for duty. He is still serving.

Comment. The severe tension and panic attacks failed to respond to modified insulin and psychotherapy. When he was admitted to the hospital, a vicious circle had apparently developed with emotional tension, accompanied by pituitary overactivity with increased production of thyrotrophic and corticotrophic hormone, resulting in increased activity of the thyroid and adrenal cortex. The increased amount of hormones released by these glands would appear to be related to the persistence of this patient's symptoms. It is known that estrogen can depress pituitary anterior lobe function. This hormone was therefore used in an attempt to interrupt the vicious circle described, and it produced a rapid restoration of hormone equilibrium associated with clinical improvement. Apparently, the application of therapy based on the biologic findings coincided with clinical improvement.

Case 4. Acute Anxiety State with Compulsive Features and Impotence. A junior noncommissioned officer, aged 20 years, married, above average intelligence, with six months of Army service, was admitted to the Royal Victoria Hospital on Sept. 14, 1954, with severe acute anxiety features. On examination the patient was very tense, anxious, and agitated. He walked with a slow hesitant step, and when asked to sit down, placed himself on the front edge of the chair, where he kept fidgeting, wringing his hands, and biting his nails. He appeared unhappy, suspicious, and frightened. He exhibited marked tremor of the lips and hands. He spoke in a dull, monotonous, soft, and petulant voice, and was clearly most reluctant to discuss his problems. His talk, however, was rational, relevant, logical, and coherent. There was no evidence of disordered thinking. His mood was one of misery and self-pity, and throughout the interview he was in tears. Mood and thought content were congruous. There was no evidence of ideas of reference or influence, hallucinations, or delusions; he was well orientated in time and place. His hands were moist, but no other physical signs were elicited.

In addition, he complained of compulsive urges to wear women's clothing, and of impotence with his wife. The former had been present since the age of 6 years when he used to sleep in his parents' bedroom and put on either his mother's or sister's underclothes. This urge to which he had succumbed had been present two or three times a week ever since. He was married six months previous to this examination to a girl who knew about his compulsion. Since then he had frequently dressed up in his wife's underclothes.

On all these occasions he would wear the garments for about 15 minutes, frequently having an erection, but he denied having any ejaculations. The wearing of these garments relieved his emotional tension, but he became harassed by thoughts that he would like to become a woman. He complained that his marriage was in danger of breaking up because his sexual relations with his wife were hopeless, and he had had no proper sexual intercourse since marriage.

The patient did well at school, obtaining a school-leaving certificate at the age of 16 years. He had had steady work as an apprentice plumber and pipe fitter before joining the Army. Until his admission to the hospital, he had had an excellent service record.

While overseas in Germany he became acutely worried about his condition and was admitted to a hospital, and then transferred to the Royal Victoria Hospital with the psychiatric opinion, "I doubt if this soldier will be able to complete his service, in view of his psychopathology which requires prolonged and skilled psychotherapy!"

Endocrinological Investigation. This patient showed an increased thyroid activity as determined by the tracer method, while his 17-ketosteroid excretion rate was slightly above normal. These findings suggested an increased activity of the pituitary anterior lobe.

Consequently, in order to depress this activity, the patient was treated with long-acting estradiol undecylate (estradiol depot, Schering) injected intramuscularly. Following this, the thyroid activity gradually came down to the normal range and the total 17-ketosteroid excretion rate also fell, but the dehydroandrosterone fraction of the 17-ketosteroid showed a rise (fig. 4).

Comment. Suppression of the pituitary activity of this patient with estradiol undecylate restored the hormone equilibrium.

The careful dosage of estrogen did not affect the patient's sex drive, but suppressed his neurotic disturbances, which were apparently related.

The endocrine disturbance in this case was very similar to that in case 3. His psychiatric disturbance, however, was more chronic, and in addition was complicated by some compulsions and by impotence. The patient was treated on the same principles as were used in case 3, the only difference being that an estradiol depot preparation was used. This long-acting preparation is of value in patients in whom injections produce additional stress that might delay the establishment of hormone equilibrium. As can be seen from figure 4,

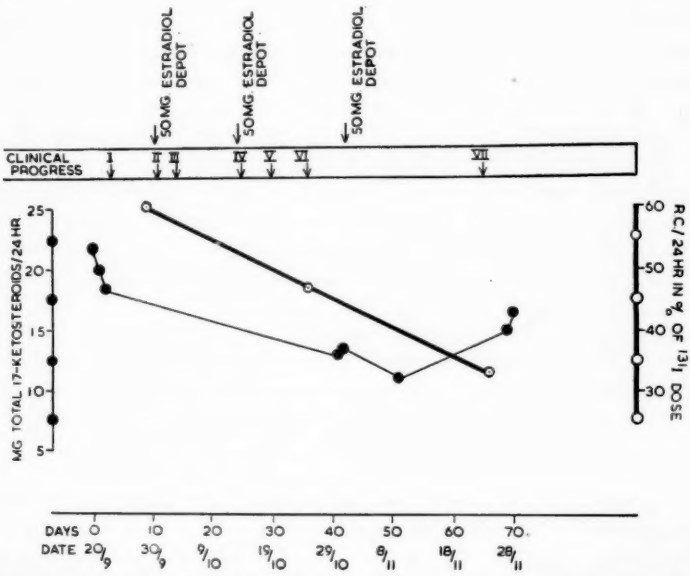

FIG. 4. Clinical progress in case 4. (I) Sept. 23, 1954—No clinical change. Malamud Rating Scale 20½. (II) Oct. 1, 1954—Patient still tense. (III) Oct. 4, 1954—Anxious, agitated, sleeping badly, poor appetite. Weepy and querulous. Malamud Rating Scale 19½. (IV) Oct. 15, 1954—Clinical condition unchanged. (V) Oct. 20, 1954—Patient happier. Sleeping and eating well. Some tension still present, absence of tearfulness. (VI) Oct. 26, 1954—Marked improvement. Patient is happy. Sits calmly without tension and states that his sexual relationships with his wife have been perfect during the week end. (VII) Nov. 29, 1954—Discharged to full duty. Malamud Rating Scale 2. (VIII) June 1, 1955—Continuous serving with no symptoms.

he had three injections during his entire stay at the hospital. In his case mental improvement accompanied the normalizing of the hormone equilibrium. In order to maintain the latter it was arranged, on discharge from hospital to unit, to give the patient one injection of estradiol depot every eight weeks. A recent review of the patient shows that improvement has been maintained and that he still retains potency.

Case 5. Acute Anxiety State in a Schizoid Personality. A National Service private with 18 months of service, aged 20 years, was admitted to a hospital in Germany on April 2, 1954, following a suicidal attempt by swallowing aspirin. He was transferred to the Royal Victoria Hospital on June 16, 1954.

On examination, he was very anxious, restless, agitated, and tense, and exhibited facial twitching and sweating of the palms. His stream of talk was relevant and rational, with some circumstantiality and a tendency to verbosity and vagueness. Concentration was impaired, and memory intact. In mood he was mildly depressed, but there was no incongruity. He was well orientated and had no hallucinations or delusions. Physically, nothing abnormal was detected.

From early childhood he had shown emotional instability and behavior disorder, necessitating frequent changes of school and outpatient psychiatric treatment. His mother was a chronic alcoholic who had been placed in a mental hospital and who eventually committed suicide. His only sibling, a younger brother, was for years under the care of a child guidance clinic.

Endocrinological Investigation. The predominant disturbance in the hormone equilibrium of this patient was a considerably increased thyroid activity; the ketosteroid excretion rate was in the upper borderline of the normal range, and the androsterone excretion rate was very high, while only very little dehydroepiandrosterone (in per cent of the total 17-ketosteroids) was excreted. The patient was treated with estradiol benzoate, 10 mg. daily, in order to reduce the thyroid activity on the basis that in association with the high excretion rate of total 17-ketosteroids, the thyroid overactivity might be due to pituitary hyperfunction. However, the thyroid activity was little affected, remaining high in spite of this treatment. No clinical change could be observed, even though the total ketosteroids decreased. For this reason, it was assumed that the increased thyroid activity in this case was a primary hyperfunction of the thyroid itself and therefore Neomercazole treatment was started, after which the thyroid activity was reduced and the excretion rate of the 17-ketosteroids remained within the normal range. Clinically the patient improved, and follow-up three months later showed that improvement was maintained. (See figure 5.)

Comment. Estradiol benzoate produced a reduction of the total 17-ketosteroid excretion rate without affecting any clinical improvement or altering the activity of the thyroid. This seemed to indicate a primary thyroid overactivity, for which Neomercazole was prescribed. The administration of the latter resulted in a gradual return of the thyroid to normal, accompanied by clinical improvement.

The patient was discharged into a quiet civilian job, and continued treatment with Neomercazole, 5 mg. daily. He has been doing very well in his job. About two months after discharge he returned to the hospital for check-up, and his thyroid activity was tested again and found to be high. However, at this time he did not show psychiatric symptoms. The only explanation for this is the fact that the stress conditions in the patient's civilian job were not now so severe as those that initially precipitated the psychiatric disturbances in association with disturbed hormone equilibrium and the reduced width of adaptation of

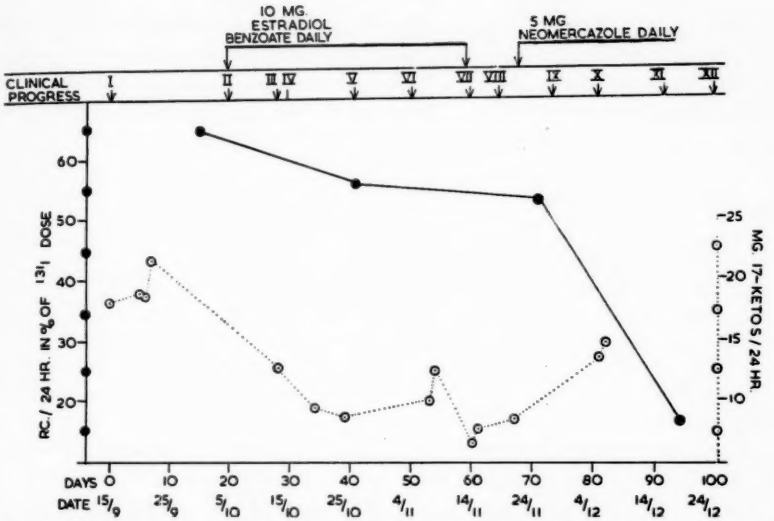

FIG. 5. Clinical progress in case 5. June 17, 1954—Appears mildly mentally depressed and agitated and exhibits flattening of affect. July 3, 1954—Clinical condition deteriorated. Transferred to closed ward. July 7, 1954—Confused, agitated. Religiously ruminative. Very emotional and tense. Deep sedation begun (Sodium Amytal, 6 gr. three times a day). July 16, 1954—Temperature 103 F.; pulse 120/minute. Clinical evidence of right-sided lower lobe pneumonia. Penicillin given—slightly more confused mentally. July 18, 1954—Initially greatly improved. Not agitated. Less anxious and tense. Pneumonia improving. July 27, 1954—Clinically improved, mentally and physically. Aug. 6, 1954—Mental condition deteriorated. He is tense, anxious and agitated, and confused. Aug. 7, 1954—Tension very severe. Emotionally very upset. Chlorpromazine ordered. Aug. 10, 1954—Chlorpromazine stopped as white blood count dropped to 2700/cu. mm. Mental condition unchanged. Aug. 16, 1954—Clinical condition improved. Allowed home two weeks under care of parents. Aug. 31, 1954—Returned from leave. More cheerful and cooperative and for first time took part in ward activities. Sept. 7, 1954—Although better than when first admitted, he is still tense, anxious, and agitated. These symptoms are easily aroused by minor stimuli.

(I) Sept. 14, 1954—Extremely tense, nervous, and distressed. Difficulty in expressing himself. (II) Oct. 4, 1954—Patient is restless and agitated. Exhibits some twitching of the face, tremors of lips and fingers. Acne on face. Emotionally labile and wept at interview. Some flattening of affect. Insomnia. Malamud Rating Scale 21½. (III) Oct. 9, 1954—No clinical change. Restless sleeper. (IV) Oct. 12, 1954—Appears happier. Subjectively feels much better. Objectively there is little difference. (V) Oct. 26, 1954—Subjectively and objectively improved. Not agitated or restless. No tremors. Sleeping better. Oct. 29, 1954—Improvement continues. Malamud Rating Scale 14. Nov. 2, 1954—Returned from leave. Very restless and agitated. Had an emotional outburst at home yesterday when he threw a cup of tea at the wall after argument with his stepmother. (VI) Nov. 5, 1954—Little improvement. Remains restless, agitated, and emotionally labile. Malamud Rating Scale 24. (VII) Nov. 12, 1954—Clinical condition unchanged. In an impulsive outburst of bad temper he threw a plate at the wall. (VIII) Nov. 19, 1954—No clinical improvement. Very nervous and tense. Continually puts his hand to his mouth when talking. (IX) Nov. 26, 1954—Clinical condition remains unchanged. (X) Dec. 5, 1954—Appears less agitated and tense. Still remains "asocial." Concentration still impaired. (XI) Dec. 18, 1954—Objectively shows clinical improvement. Less anxious. Optimistic about his future and very sociable. (XII) Dec. 23, 1954—Discharged from hospital much improved. Feb. 10, 1955—Patient appears confident and happy and exhibits no clinical evidence of any psychiatric disability.

this patient. His present occupation is in better harmony with the reduced adaptability of this patient. A further check showed that the thyroid activity is now well within the normal range, and this patient's clinical improvement is maintained. This was confirmed by a recent communication from his father. He is on a maintenance dose of Neomercazole, 5 mg. every third day, and will be rechecked at intervals.

DISCUSSION

In this paper, 5 patients are described who had a variety of psychiatric symptoms that were accompanied by disturbances in hormonal equilibrium in which a predominance of thyroid deviations was demonstrated. Common to all were signs and symptoms of anxiety, while the predominant thyroid deviation in each was overactivity. Hemphill[5] draws attention to the fact that anxiety is generally believed to be basically responsible for hyperthyroidism, unless the picture is colored by delirium derived from excessive thyroid intoxication. In the 5 cases presented here, there was nothing clinically to suggest hyperthyroidism and in none was there any evidence of thyroid enlargement. It is relevant to point out that investigations of thyroid function in the male mental hospital population of Bristol indicate a definite tendency to hypothyroidism.[14] It is, of course, extremely difficult to decide on causal relationships between endocrine disturbance and psychiatric symptoms, owing to the complexity of the various factors concerned with mental breakdown. The precipitating cause may be primarily responsible for the change in endocrine equilibrium. Or, the endocrine equilibrium may have been initially disturbed so that mild precipitating factors produced mental breakdown because of the narrow adaptation of the individual, whose vulnerable basic personality could not stand up to additional small stresses that are resisted by others without difficulty. We are in agreement with Hemphill[6] that the demonstration of undeniable endocrine disturbances does not authorize the claim that they have a causal relationship with mental symptoms. These few cases merely indicate a relationship between psychiatric symptoms and overactivity of the thyroid in which the restoration of hormonal equilibrium coincided with recovery of the mental symptoms.

Cases 1 and 2 show similar peripheral undersensitivity to thyroid, the pathogenesis of which is not yet known. This state has not been reported in other than psychiatric patients.[4]

Patients showing peripheral undersensitivity to thyroid hormone appear to suffer in effect from a mild form of hypothyroidism. Their tissues are unable to increase the rate of oxidation sufficiently whenever necessity arises (e.g., change of temperature). It is possible that such a reduced capacity to utilize thyroid hormone acts like any other hormone deficiency in the periphery, and it is apparently due to the neuroendocrine feed-back mechanism that more thyrotrophic hormone is produced under such conditions. It is believed that an equilibrium is preserved between the anterior pituitary and the thyroid through the concentration of thyrotrophic and thyroid hormones in the blood. Thyrotrophic hormones increase the secretory activity of the thyroid, but the thyroid hormone inhibits the thyrotrophic activity of the anterior lobe of the pituitary.[9]

It might well be that in the 2 cases described above the peripheral undersensitivity for

thyroid hormone was the primary cause for the thyroid hyperfunction found. Such an assumption gets some support from the fact that the thyroid activity in case 1 was reduced to normal range by treatment with nicotinic acid only.

Neither of these 2 patients showed any clinical symptoms of vitamin deficiency. Gregory[3] has comprehensively reviewed the action of nicotinic acid, and has pointed out the multitude of conditions in which nicotinic acid can be used beneficially in psychiatry. The action of this substance on the peripheral hormone undersensitivity described may indicate an important role of this substance in endocrine equilibrium.

Case 4 shows how careful one should be in the endocrinologic approach to the symptoms of impotence. The present-day practice of those attempting the cure of impotence is to use psychoanalysis or to experiment with the use of the male sex hormone. It is seldom that disturbances of other glands are considered; in particular,[9] it would seem appropriate to investigate the thyroid function in cases of impotence when such patients excrete 17-ketosteroids in or above the normal range.

When surveying the endocrinologic investigations carried out on these patients, it should be emphasized that they still represent only initial attempts in endocrine investigations to analyze the psychoneuroendocrine interrelation. Estimation of the corticoids of these patients could not be carried out systematically; so the investigation of the adrenal cortex activity must be regarded as incomplete since 17-ketosteroid results indicate changes in only some of the adrenal cortex functions. Further, it would have been valuable to determine the concentration of the pituitary anterior lobe hormones in the body fluids instead of making only indirect deductions about their production, but routine methods are not yet available, being still in the developmental stage. Nevertheless, this restricted investigation of the changes in the thyroid gland and adrenal cortex associated with psychiatric changes appears to throw some further light on the significance of the endocrine equilibrium in psychiatric disturbances. Although this paper describes a number of cases with varying psychiatric disturbances treated on the basis of endocrinological investigations, we would stress that we are not advocating any general hormonal therapy in such cases but only attempt to describe a logical approach to a rational treatment, rather than one resting on an empiric basis, as is so common in psychiatry today. Furthermore, it should be stressed that no such therapy should be attempted unless investigations indicate that their use may help to restore biologic equilibrium. The latter is, however, only one among many factors found disturbed in mental illness. This is important since the restoration of biologic function greatly assists the psychiatrist in maintaining a progressive psychotherapeutic rehabilitation program and helps the patient to face up to his problems and adjust better to his environment.[15]

SUMMARY

Overactivity in the thyroid gland in association with varied psychiatric symptoms is described.

Patients were treated on the basis of their metabolic disturbances.

Clinical progress was correlated with changes in the function of the thyroid and adrenal cortex.

RESUMEN

Siempre que se hallen alteraciones de las características endocrinas normales, es posible normalizar el trastorno endocrino en algunos pacientes y estudiar el efecto de tales cambios en la reacción mental del paciente. En este trabajo se describen cinco pacientes con síndromes psiquiátricos en los cuales se observaron trastornos endocrinos coexistentes y para los cuales se administró la apropiada terapia hormonal, habiéndose estudiado los efectos sobre los progresos clínicos en cada caso. Las investigaciones de la actividad tiroidea fueron llevadas a cabo por el método especial para seguir el curso de las sustancias radioactivas. La gran ventaja que tiene este método sobre el de la determinación del porcentaje del metabolismo basal, estriba en su propiedad para descubrir los límites de los trastornos de la función tiroidea.

RESUME

En présence de déviations du cours normal endocrin, il est maintenant possible de normaliser chez certains patients les troubles endocrins et d'étudier l'effet de tels changements dans la réaction mentale du sujet. On présente cinq patients avec syndromes psychiatriques chez lesquels il y eut des troubles endocrins concomitants et pour lesquels une thérapeutique hormonale appropriée a été donnée et les effets du progrès clinique étudiés dans chaque cas. Des recherches sur l'activité thyroïdienne ont été faites par la méthode de radio-activité des corps marqués. Le grand avantage de cette méthode sur celle de la détermination du taux métabolique basal est sa convenance à découvrir des cas limites de troubles de la fonction thyroïdienne.

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Psychiatric Implications of Sex Differences in Thyroid-Histamine Interrelationship

A Clinical and Laboratory Study*

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A postulated schema of hormonal equilibrations, based upon clinical and physiologic observations, has been presented in previous communications.[1, 2] In this conception, an antidyne (reciprocal antagonist) relationship or reversible equilibrium between the adrenal glucocorticoid hormones on the one hand and the hormones of the thyroid and gonads as well as insulin and histamine on the other is viewed as a basic phenomenon in normal physiology. One derivative of this conception is that an imbalance or dysequilibration between these two sets of hormones, permitting the catabolic effects of adrenocorticalism to disrupt neuronal functioning, can be conceived as an etiologic factor in mental disease.

It has also been suggested that this hyperadrenocorticalism could be due to one of three possible types of imbalance: (1) absolute excess of the circulating adrenal hormones without a compensatory rise in the antidynes; (2) relative hypercorticalism (normal level of adrenal hormones with a decreased level of the antidynes); and (3) operative hypercorticalism (a hypersusceptibility of the end organs, in this case probably the neurons, to adrenocortical effect without a compensatory increase in either antidyne level or in susceptibility to the antidyne effects). Combinations of two of these types of imbalance or of all three could also coexist. This concept made it possible to predict that cortisone and ACTH would precipitate psychoses in some individuals, a prediction that has been amply confirmed by clinical experience, and it suggested the use of additional antisympatheticoadrenocortical substances, e.g., testosterone and progesterone, as biochemotherapeutic agents in the management of some psychiatric patients. The present report is an extension of these earlier investigations and presents the role of the thyroid gland in the pattern of physiodynamic interrelationships. It further offers additional data pertinent to the role of hormonal dysequilibration in schizophrenia.

BACKGROUND

In earlier publications[3–5] attention has been directed to the tolerance of schizophrenics for massive doses of thyroid substance. This tolerance was tentatively attributed to an altered physiologic milieu characterized by hyperadrenocorticalism. A similar disturbance

* This paper was presented at the Fourth Creedmoor Conference at Creedmoor State Hospital, Queens Village, N. Y., December, 1951.

in equilibration has been proferred to explain the high tolerance of a significant proportion of schizophrenics for other physiologic substances, e.g., histamine and insulin, and for such pharmacologic agents as morphine, barbiturates, and alcohol. Preliminary exploration[4, 6, 7] revealed that the administration of thyroid substance to schizophrenics reduced their tolerance to histamine. Other related observations include:

1. The clinical picture of the hebephrenic suggests a combination of the mental retardation and behavior of extreme hypothyroidism together with the bizarreness of schizophrenia.[10]

2. A tendency to low thyroid function in hebephrenics has been reported by Brody and Man[11] and Bowman et al,[12] and Reiss et al[13, 14] have reported a significantly higher iodine uptake and lower basal metabolic rate in schizophrenics.

3. Thyroid dysfunction, as evidenced by increased iodine uptake, in mothers of schizophrenic children has been reported by the present workers.[8, 9]

4. Increased output of thyrotropic hormone has been demonstrated by Hemphill and Reiss[15] to be induced by electroconvulsive therapy.

5. Cortisone has been found to raise the blood cholesterol level[16] and depress the basal metabolism.[17]

6. The failure of schizophrenics to respond to epinephrine stimulation has been shown to be corrected by the administration of thyroid hormone.[18]

Originally, clinical observations and physiologic findings provoked the hypothesis that hypothyroidism (relative or absolute) with concomitant relative and operative hyperadrenocorticalism was a possible etiologic and pathogenetic factor in at least one subgroup of the schizophrenias.

The present work is part of the clinical and experimental studies designed to test the validity of certain of these neuroendocrinologic formulations (1) by studying clinically the tolerance of schizophrenics to thyroid substance and to histamine, as well as to histamine following thyroid medication, and (2) by studying experimentally the tolerance of thyroparathyroidectomized rats to histamine as compared to that of the intact animal and the tolerance of the female thyroparathyroidectomized rats to histamine as compared to that of the similarly operated on male animal.

CLINICAL STUDIES

Experimental Design, Material, and Methods. Clinical studies were directed toward the determination of (a) histamine tolerance, (b) thyroid tolerance, and (c) the effect of thyroid medication upon histamine tolerance.

The clinical population for this part of the study was comprised of 15 adult hospitalized schizophrenics ranging in age from 23 to 45 years. After completion of the basic laboratory tests, initial histamine tolerance was determined.

The laboratory tests to establish base line parameters were performed over a three week period prior to the institution of therapy. The tests included determination of blood pressure and pulse rate daily, serum cholesterol, complete blood count and sedimentation rate once weekly, and direct eosinophil count daily for the first week and three times a week thereafter.

Histamine tolerance was determined for each patient in the premedication period. The measure of tolerance was that amount of histamine base required to induce on three successive days a diastolic blood pressure of 0, i.e., the persistence of the heart sound or the failure of change in the quality of that sound even when applied pressure at the cubital fossa reaches 0 as determined by cuff sphygmomanometry. In the test procedure for histamine tolerance, histamine phosphate dissolved in sterile water was administered subcutaneously (3 patients started with an initial dose of 0.2 mg., 12 with 0.5 mg.); on each successive day, five days a week, the dosage was increased by 0.2 mg. (histamine base) until the criterion for tolerance was achieved. Following each injection, blood pressure and pulse rate were read at five minute intervals for a minimum period of 15 minutes.

After the above pretreatment tests, the 15 patients were subdivided into groups of 5 patients each, matched as closely as possible in age, body build, and duration of illness. One group received thyroid medication, a second propylthiouracil, and the third, placebos, each for a period of approximately 12 weeks. The measure of thyroid tolerance was that amount of thyroid substance required to increase the resting pulse to a rate of 100/minute during the postabsorptive state. In the test procedure for thyroid tolerance, thyroid sub-

TABLE I

Effect of Thyroid on Histamine Tolerance

Pt.	Age	Prethyroid tolerance to histamine, mg. (histamine base)	Total accumulative thyroid dose, Gm.	Maximum dose of thyroid received, Gm.	Post-thyroid tolerance to histamine, mg. (histamine base)	Change, %
1	41	4.0	69.5	2.1	1.1 (3 zeros)	−72
2	29	2.3	65.3	2.0	0.5 (3 zeros)	−78
3	45	3.5	44.6	1.7	3.7 (no thyroid during histamine, B.P. 50/30, pain)	6
4	24	2.3	46.3	1.7	1.3 (B.P. 70/40, precordial pain)	−43
5	29	2.1	63.3	2.0	0.5 (3 zeros)	−76
6	39	4.5	23.9	1.3	1.5 (irregular pulse, skipped beat at 1-2 hr.)	−67
7	33	2.4	67.5	2.1	0.9 (3 zeros)	−62
8	27	3.1	69.5	1.9	0.9 (3 zeros)	−71
9	44	5.1	77.7	2.0	1.7 (3 zeros)	−67
10	30	1.7	20.5*	0.8	0.6 (B.P. 160/64, rise in B.P., histamine tolerance discontinued)	−65
11	30	2.1	30.6	1.4	1.6 (3 zeros)	−24
12	44	3.3	71.6	2.1	1.1 (2 zeros)	−67
13	24	2.7	61.0	1.9	1.5 (1 zero, pallor, cyanosis, 0_2)	−44
14	23	1.9	63.2	2.0	0.6 (3 zeros)	−68
15	31	2.7	62.6	2.0	1.1 (B.P. 80/60, irregular pulse, seen by M. D. S.)	−59

* Went up to 20.5 then decreased daily by .0324 Gm.

stance was administered every morning as Proloid tablets, starting with a dose of 60 mg. (1 gr.) and increased by 30 mg. daily five days a week. At the termination of each treatment period, histamine tolerance was re-evaluated. The therapies were then rotated so that each patient was under study during an over-all period of approximately 55 weeks.

Results: Table I shows that the dosage range for histamine tolerance before thyroid administration was between 1.7 and 5.1 mg. of the base, with a mean of 2.9 and a median of 2.7 mg. The range of the maximum dosage of thyroid substance administered without evoking undue physiologic disturbance was between 0.8 and 2.1 Gm., with a mean of 1.8 and a median of 2.0 Gm. However, hyperactivity, restlessness, and increased verbal productivity have been noted in some of these patients receiving massive thyroid dosages. The reduction in histamine tolerance effected by thyroid administration is manifested by a post-thyroid histamine tolerance ranging from 0.5 to 3.7 mg., with a mean of 1.2 and a median of 1.1 mg., a reduction of from 59.3 to 72.5 per cent below the prethyroid levels. In only 1 case was a slight increase of 6 per cent registered, while in 14 there was a decrease of from 24 to 78 per cent.

ANIMAL STUDIES

Material and Methods. Two hundred twenty-five young adult Wistar albino rats were placed in two groups: (a) the controls consisted of 58 intact males and 44 intact females, and (b) the thyroparathyroidectomized group consisted of 53 males and 70 females.

In determining the histamine $L.D._{50}$, each animal was injected intraperitoneally in a single dose with histamine phosphate (10 per cent solution in distilled water). This was calculated by the method of probits and is the dose of histamine base required to cause death in 50 per cent of the animals treated. The thyroparathyroidectomized animals were subjected to testing of histamine $L.D._{50}$ four to six weeks postoperatively. In order to minimize extraneous factors such as seasonal variations, animals from each group were injected on the same day whenever possible, dosage being recorded as milligrams of histamine phosphate/Kg. of body weight.

Results: In the control group, the histamine $L.D._{50}$ was found to be 1250 mg./Kg. in the female and 1245 mg./Kg. in the male. The difference in the histamine $L.D._{50}$ between males and females is not statistically significant, and the pattern of response to histamine appears to be the same in both sexes (table II and fig. 1).

In the thyroparathyroidectomized group, the histamine $L.D._{50}$ was markedly increased by thyroparathyroidectomy: in the female to 1899 mg./Kg., an increase of 52 per cent, and in the male to 1623 mg./Kg., an increase of 30 per cent. The sex difference in the histamine $L.D._{50}$ following extirpation of the thyroid (and parathyroids) is statistically significant, and the pattern of response to histamine is also apparently affected in that the slopes are significantly different (table III and fig. 2).

DISCUSSION

It may be worth while at this point to assemble the diverse evidence for the antidynal

TABLE II

Histamine Tolerance of Intact Male and Female Rats

Dose, mg./Kg.	Number injected	Number died	Per cent died
*Male**			
1100	2	—	—
1200	10	3	30
1250	10	6	60
1300	10	7	70
1450	10	9	90
1500 and higher	16	16	100
Female†			
1100	2	—	—
1200	18	13	28
1250	10	5	50
1300	10	7	70
1450	3	3	100
1500	1	1	100

* The L.D. $_{50}$ was 1245 mg./Kg.; 95 per cent range, 1196–1298.

† The L.D.$_{50}$ was 1250 mg./Kg.; 95 per cent range, 1215–1286.

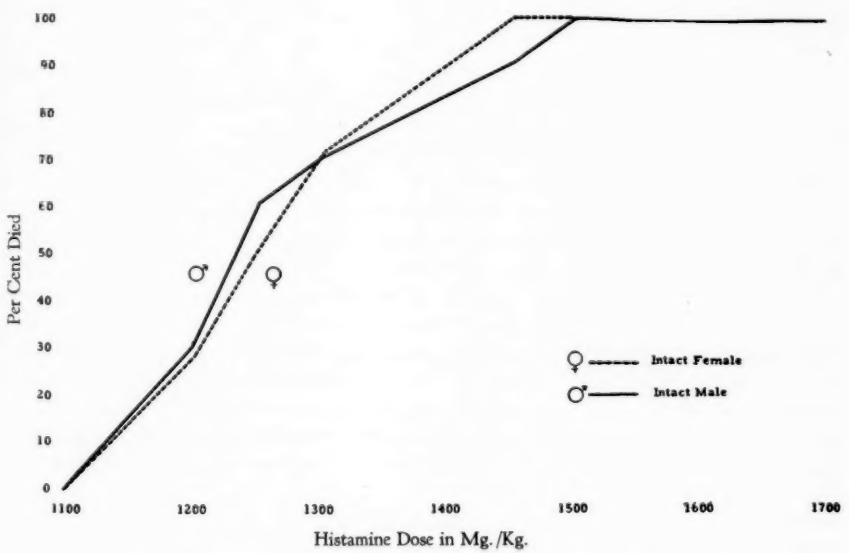

FIG. 1. Histamine phosphate dosage mortality relationship in intact albino rats.

TABLE III

Histamine Tolerance of Thyroparathyroidectomized Male and Female Rats

Dose, mg./Kg.	Number injected	Number died	Per cent died
*Male**			
1400	4	—	—
1450	4	1	25
1500	10	3	30
1550	6	3	50
1600	10	5	50
1700	6	4	67
1800	7	4	57
1900	2	2	100
2000	4	4	100
Female†			
1400	2	—	—
1500	5	—	—
1600	7	1	14
1700	6	1	17
1800	10	2	20
1850	10	4	40
1900	10	5	50
1950	10	6	60
2000	6	5	83
2100	4	3	75

* The $L.D._{50}$ in male rats was 1623 mg./Kg.; 95 per cent range, 1540–1710.
† The $L.D._{50}$ in female rats was 1899 mg./Kg.; 95 per cent range, 1827–1973.

effect of thyroid hormone on adrenocortical function. This makes it possible to explore the role that hormonal dysequilibration of this type may play in the causation of psychosis in a given patient and to attempt to construct a hypothetic pattern of interaction.

Thyroid-Adrenocortical Antidyne Activity. Clinically, investigators have discussed the importance of physiologic suppression of thyroid activity by the adrenals and gonads. Various aspects of a thyroid-adrenocortical relationship have been reported by Zondek,[19] Kaelsche and Kendall,[20] Talbot et al,[21] Hill et al,[22] Wallach and Reineke,[23] Hardy et al,[24] Freedman and Gordon,[25] Money et al,[26] and Pekkarinen.[27] Means[28] and Hill et al[22] have expressed the belief that hyperthyroidism may be related to lowered adrenocortical function and possibly increased lymphoid activity.* In this connection it may also be

* Additional support may also be derived from observations of the greater susceptibility to shock in hyperthyroidism and the higher incidence of allergic phenomena in hyperthyroidism (as against its low incidence in schizophrenia).

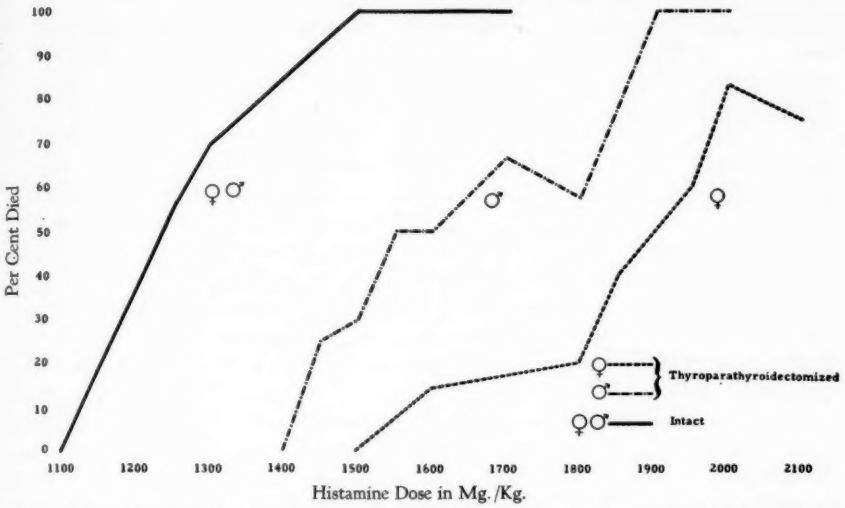

FIG. 2. Effect of thyroparathyroidectomy on histamine phosphate dosage: mortality relationship in albino rats.

mentioned that a lymphocytosis occurs in hyperthyroidism while a lymphopenia accompanies cortisone action. Hill et al[22] recently reviewed evidence pointing to a protective action of adrenocortical steroids against thyroid intoxication. Finally, it has been reported that administration of large quantities of cortisone and ACTH to patients with collagen diseases has resulted in production of hypothyroidism.[29]

In our own experimental work on the antidynal relationship between adrenocortical hormone and thyroid, histamine has been used as a test substance. Other workers[30, 31] have demonstrated a reciprocal antagonism between histamine and the adrenal glands, and our own previously reported experimental work on the marked decrease of the histamine L.D.$_{50}$ caused by removal of the adrenals appears to support this relationship. Assuming that the increase of the histamine L.D.$_{50}$ in thyroparathyroidectomized rats was due solely to the removal of the thyroids, this antidynal relationship again seems to hold; the data also suggest a sex differential in thyroid function.

Thyroid Function in Schizophrenia. Kraepelin,[32] over 60 years ago noted thyroid alterations and their possible metabolic contribution to psychiatric disorders other than those associated with cretinism and myxedema.

Of further interest are the cases of "myxedematous madness" reported in the English literature,[33, 34] the not infrequent occurrence of psychosis following thyroidectomy,[35–38] and the enlargement of the thyroid concomitant with psychic disturbance at the time of menstruation, pregnancy, and menopause.

Brody and Man[11] reported that, even after first eliminating from the group under study all patients with demonstrable thyroid dysfunctions, the hebephrenic schizophrenic still showed a tendency to low thyroid function. Bowman et al[12] noted that schizophrenics had

a significantly higher iodine uptake and significantly lower basal metabolic rate than the controls. In addition, serum protein-bound iodine was found to be normal These authors suggested: (1) a qualitative defect in circulating thyroid hormone impeding oxygen consumption in tissues or (2) a lowered oxygen consumption in schizophrenics unrelated to thyroid function. As to high uptake of radioactive iodine, Bowman's group raised the question as to borderline functioning of the thyroid gland "without any reserve to withstand stress," or simply, "a sympathetic 'hyperactivity' and instability of the gland, sympathetic or endocrinologic."[12] Reiss et al[13] reported that acute female schizophrenics evince increased thyroid function as measured by iodine uptake, while chronic schizophrenics show no deviation or even subnormal iodine uptake.

In our own clinical studies we have shown that the schizophrenic has a high tolerance for histamine and for thyroid hormone, both presumably "antiadrenocortical" agents. Secondly, treatment with thyroid hormone effects a significant reduction of histamine tolerance.

These findings could well be related directly to an operative excess of adrenocortical substance or indirectly via cellular or peripheral mechanisms. The lowered histamine tolerance during thyroid administration may result from a "reduction" in available adrenocortical substance without necessarily a change in absolute concentration (directly or indirectly). Finally, we have found abnormal radioiodine uptake accompanied paradoxically by normal or low basal metabolic rates in 8 out of 17 mothers of schizophrenic children, suggesting thyroid dysfunction of a special type. This pathophysiology is associated with clinical psychiatric and/or psychologic test findings of schizophrenia, either arrested or compensated, in a majority of these same mothers. The association of psychopathology and endocrine pathology in the mothers of these patients and its relation to the disturbance in the child, which has been discussed in previous articles, is worthy of further study.

In schizophrenia, the low basal metabolic rate, the high thyroid tolerance, and the high histamine tolerance, lowered by administration of thyroid, are consistent with a functional hyperadrenocorticalism whether absolute, relative, or operative. The reportedly increased iodine uptake, the increase in serum precipitable iodine, and the occurrence of a normal to low basal metabolic rate are not necessarily inconsistent with this view.

Sex Differences. The sex difference in incidence of schizophrenia in childhood, adolescence, and adulthood may very well be related to a difference in thyroid activity in the human male and female. We have discussed in previous presentations the more frequent occurrence of psychopathology in male than in female children and the shift in sex incidence as regards psychiatric disturbances in the older groups. The clinical possibility suggested in our experimental animal data that the thyroid of the female has relatively greater functional capacity may help explain the lower incidence of schizophrenia in female children and the greater susceptibility of the male child to endocrine dysequilibration. At pubescence a change begins to be noted in the sex incidence of schizophrenia, and the incidence in the female begins to rise. At the involutional period the incidence of the disease in both sexes is approximately the same. This change in incidence with increasing age may be associated with greater demands on thyroid function in the female and an operative hyperadrenocorticalism, uncompensated by either thyroid or gonadal, or possibly thymic, antidyne

action. Such endocrine imbalance could possibly lead to physiopathology with associated psychopathology.

Further, the relative incidence could also be influenced during pubescence in the male by the greater production of testicular hormone with its relatively greater "anti-adrenocortical" effect and at involution to the decreased production of testicular hormone.

Viewed functionally, one would expect that some mechanism must exist to balance out this sex differential in thyroid function. Our further work suggests that the thymus in childhood and perhaps the gonads in adult life help serve this purpose.

Physio-Psycho-Dynamic View of Hyperthyroidism. Hyperthyroidism is a psychosomatic disorder with markedly higher incidence in women than in men. This sex predilection, as well as the higher incidence of other thyroid disorders in women, is consistent with the experimental evidence of a greater thyroid role in female rats. For, a gland with greater activity would logically be expected to be more susceptible to pathologic processes. This disease has been studied by many workers from both a physiologic and psychodynamic orientation. There is general agreement that it is associated with psychogenic factors and usually becomes manifest following emotional disturbances accompanied by fear and anxiety.

In the physiodynamic perspective outlined in this work one may view the clinical picture of the development of hyperthyroidism as an expression of the inability of an organism to attain equilibration during reduction of sympatheticoadrenal overactivity when the emotional disturbance that has evoked the hyperactivity has subsided. A smooth synchronous reduction of endocrine functions, which perhaps occurs in most individuals subjected to stress, would permit re-establishment of equilibration. Instead, in these individuals there then apparently occurs faulty or uneven involution of function from the high plane required by the chronic anxiety-producing external environment. In a sense, this is the converse of the production of an Addisonian crisis by the administration of large doses of thyroid substance to a myxedematous patient.

This physiodynamic endocrine viewpoint takes into account the psychogenic influence that catapults the patient into a higher plane of function. In addition, it highlights the fact that a faulty endocrine constellation in some individuals at certain times produces the clinical picture as we know it. This physio- and psychodynamic interpretation receives suggestive support from the data reported herein.

SUMMARY AND CONCLUSIONS

1. Schizophrenics tolerate high doses of histamine and massive doses of thyroid.

2. The administration of thyroid hormone reduces histamine tolerance significantly in both hospitalized and nonhospitalized schizophrenics.

3. The histamine $L.D._{50}$ in Wistar albino rats is increased by 52 per cent in females and 30 per cent in males after thyroparathyroidectomy. This finding not only suggests a role of the thyroid in reciprocal antagonism to that of the adrenal cortex but also a sex differential in this function.

4. The findings reported in this work and pertinent clinical observations on the interrelationships between thyroid and adrenal function have been woven together in a physio-

dynamic concept having a bearing on hormonal equilibration, on the role of the thyroid in schizophrenia, on the sex differential in the incidence of schizophrenia at different stages of life, and on a new perspective in the development of hyperthyroidism.

RESUMEN

Los esquizofrénicos toleran altas dosis de histamina y dosis masivas de tiroides. La administración de la hormona tiroidea reduce en forma significativa la tolerancia a la histamina en los esquizofrénicos tanto hospitalizados como ambulatorios. La DL_{50} de histamina en ratas albinas Wistar, aumenta en un 52 por ciento en machos y en un 30 por ciento en hembras, después de la tiroparotiroidectomía. Estos hallazgos no sólo sugieren que el papel del tiroides es inverso al de la corteza suprarrenal, sino también una diferenciación sexual en su función. Los datos comunicados en este trabajo y las observaciones clínicas sobre la correlación entre el tiroides y la función suprarrenal, han sido integradas en un concepto psicodinámico, de influencia sobre el equilibrio hormonal, sobre el papel del tiroides en la esquizofrenia, sobre la diferenciación sexual en la incidencia de la esquizofrenia en distintas etapas de la vida, y sobre una nueva perspectiva del desarrollo del hipertiroidismo.

RESUME

Les schizophrenes tolerent de hautes doses d'histamine et de doses massives de thyroïde. La tolérance de l'histamine chez les schizophrènes hospitalisés aussi bien que chez les non-hospitalises est sensiblement réduite par l'administration d'hormone thyroïdienne. A la suite de l'excision de glandes thyroïde et parathyroïde, la dose lethale/50 chez les rats albinos Wistar est augmentée de 52 pourcent chez les mâles et de 30 pourcent chez les femelles. Cette observation suggère pour la thyroïde un rôle, non seulement contraire à celui du cortex surrénal, mais aussi une différence de fonction selon le gene. Les observations rapportées dans cette étude et des observations cliniques sur les rapports entre la fonction thyroïdienne et surrénale ont été rassemblées dans un concept physiodynamique portant sur l'equilibre hormonal, le rôle de la thyroïde dans la schizophrenie, la différence selon le gene dans l'incidence de la schizophrénie à differentes periodes de la vie, et un nouvel aperçu sur l'évolution de l'hyperthyroïdisme.

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QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

Incorporating the International Record of Psychiatry and Neurology

International Editorial Board

INCORPORATING INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY

FOREWORD

The purpose of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY is to present promptly brief abstracts, noncritical in character, of the more significant articles in the periodical medical literature of Europe and the Americas.

For readier reference, the abstracts are classified under the following general headings:

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1. Administrative Psychiatry and Legal Aspects of Psychiatry
2. Alcoholism and Drug Addiction
3. Biochemical, Endocrinologic, and Metabolic Aspects
4. Clinical Psychiatry
5. Geriatrics
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In fields which are developing as rapidly as are psychiatry and neurology, it is obviously impossible to abstract *all* the articles published—nor would that be desirable, since some of them are of very limited interest or ephemeral in character. The Editorial Board endeavors to select those which appear to make a substantial contribution to psychiatric and neurologic knowledge and which promise to be of some general interest to the readers of the REVIEW. Some articles, highly specialized in character, or concerning a subject already dealt with in an abstract, may be referred to by title only at the end of the respective sections.

A section entitled INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

The Psychiatry and Neurology Newsletter was compiled by Doctors Leon Epstein and Francis N. Waldrop.

The Editorial Board at all times welcomes the suggestions and criticisms of the readers of the REVIEW.

WINFRED OVERHOLSER, M.D.
Editor-in-Chief

ABSTRACTS

psychiatry

ADMINISTRATIVE PSYCHIATRY AND LEGAL ASPECTS OF PSYCHIATRY

78. *Explanation and Consent in Medical, Particularly Psychiatric Treatment (Die Aufklaerung und Einwilligung bei der aerztlichen, besonders der psychiatrischen Behandlung).* HANS GOEPPINGER, Heidelberg, Germany. Fortschr. d. Neurol., Psychiat. *24*:54–107, Feb., 1956.

The decision on July 10, 1954, of the *Bundesgerichtshof* (BGH) in Germany dealing with the appeal of a patient who had suffered a fracture of the spine during electroshock therapy, with subsequent paralysis of the right leg and intestinal and cardiac symptoms, produced great insecurity among physicians regarding the use of therapeutic measures. Germany is about to review its laws governing the care of the mentally ill, and there is considerable divergence of opinion among physicians and the legal profession.

The BGH demands that an explanation be given to the patient of the typical dangers existing in a proposed treatment. It considers spinal fracture a typical danger of electroshock therapy and rules therefore that the treatment without previous explanation to the patient was unlawful. The increased emotional burden that the explanation may cause the patient must be accepted as unavoidable. The *Oberlandesgericht* (OLG) of Frankfurt considers the danger of delay of treatment that may be brought about by explanation in cases of endogenous depression and states that the explanation in such cases should be of a general nature.

In regard to the medical profession, the physician, in the interest of the patient, will not always give a full explanation of the danger. The extent of the explanation always has a reciprocal relationship to the seriousness of the illness and to the extent of the expected improvement. Each physician will keep in mind the damage that might result from explanation in a particular case. With psychotic cases, it would be advisable to inform the patient of the proposed treatment and give an explanation of a general nature only, at times none at all.

As to the need for consent of the patient for a given treatment, there is not always agreement between the physician and the jurist. According to the jurist, the physician has no right, with very few exceptions, to give any kind of treatment without permission of the patient if the latter is competent to make a decision, even if delay would prove dangerous to the patient. The court emphasizes that it is the duty of the physician to respect above all the patient's freedom of decision in regard to any aggression against his physical integrity. If a patient arrives for treatment in a condition that renders him incapable of making a

decision, the physician is guided by whether there is danger in delay. If there is no danger, then treatment without permission is unlawful, even in an incompetent patient.

A special question is whether the permission of a psychotic patient could be legally binding. The author considers the permission for a treatment or the refusal valid when the patient understands the type and purpose of a projected treatment and can evaluate its meaning. A written permission is not necessary. Consent is considered given, and as legally binding, when the patient (also psychotic) shows a willingness to submit to treatment (if he lies down for injection or shock treatment). In psychotic patients the physician will have to decide in each individual case when there is danger in delay and whether a patient is at a given time competent to make a decision or not.

Two possible solutions would be legally correct and also satisfactory from the standpoint of the patient. The one adopted as law in Bavaria authorizes treatment of patients when in hospitals. The other recommendation is to give relatives of the psychotic patient the right to give legally binding permission concerning his treatment, regardless of whether the patient entered the hospital voluntarily or against his will.—*E. H. Friedman, M.D.*

79. *The Concept of Responsibility.* J. E. MACDONALD, Essex, England. J. Ment. Sc. *101*:704–717, July, 1955.

The problem of responsibility is properly not a medicolegal but a philosophic-psychologic one. Many notions still held about responsibility derive from a background of body-mind dualism, together with the archaic faculty psychology recognized in legal discussion or the outmoded Freudo-McDougallian psychology popular in certain psychiatric circles. These notions are based on the assumption that people possess some "faculty" of "self-control," which suffers impairment according to degree of psychologic abnormality; indistinguishable from "free will," it is assumed to be correlated with responsibility. Such notions are supported by neither logical argument nor psychologic evidence—they are, in fact, fundamentally illogical. Practical consequences of this way of thinking are seen in the courts when opposing psychiatrists argue the sanity of the accused, or show concern with their "contribution to the problem of punishment," and in the M'Naghten rules, which embody the tendency to look not *at* but *past* the behavior of the individual in search of some ill defined, nebulous mental kink.

Modern psychology is deterministic, monistic, behavioristic. If we know the biosocial matrix of any personality, then we know the factors that have determined his conduct, be it criminal or other as defined by social mores. The intrusion of such an arbitrary agent as "free will"—which does not mean anything, if you stop to think about it—would make a chaotic world in which scientific analysis would be impossible. In practice, however, the complexity of personality and the infancy of psychology frequently make our attempts to identify the springs of specific acts quite vain.

Recent philosophy shows that many of the problems that exercised older philosophy depend on the nature of language and not on the phenomena ostensibly being treated. Among these fall questions of "body-mind" relationship and "free will," whence comes the common notion of responsibility. It is "the ghost in the machine" that is held responsible for the individual's conduct, or misconduct. If it was a sick ghost at the time of the mis-

conduct, say the forensic pundits in effect, then it may be excused punishment; a very young or very drunk ghost may also be treated magnanimously; otherwise it is culpable. It is evident that, for those who think in the conventional, lawless, ghost-in-the-machine framework, it is only when there is some striking factor in the individual's history, obvious to laymen—as in some cases of gross mental disease or deficiency, drunkenness, or infanticide—that responsibility is to be regarded as diminished and psychologically operative factors are to be recognized; in other cases, it is the ghost. Thus the allocation of responsibility is tied to the jury's microscopic understanding of psychology. Healthy ghosts are free; sick ones are determined—this is the crux of the matter. This curious view, that only in disease and not in health do psychologic factors work, is reflected in several dichotomies: conscious-unconscious, responsible-irresponsible, free-determined, inhibited-uninhibited.

The ideas of "free choice" and "alternative" possibilities result from confusion of logical categories and misunderstanding of the epistemologic status of words and concepts. The existence of such terms and constructions in our language is a function of the fact that often we cannot predict with certainty, for lack of knowledge, and must talk about "possibilities" that do not exist in "the external world of reality" but only in our symbolic systems, i.e., hypotheses we have formulated, to which we may attach varying degrees of probability, being ignorant of which one coheres with reality. It does not follow that "there is no morality"—this is a "pseudo-object statement"—but that "morality," like other words, has no unique meaning, its meaning depends on context, and circumstances now indicate that a new usage is required.

The jury's task should be to determine whether the accused is physically responsible for the offense; if he has been found so, then his behavior has been abnormal, by its infrequency of occurrence, and impartial psychiatric examination is indicated—without need of any concept of medicolegal responsibility, which can be abandoned, as in Sweden, where disposal is no different in kind from that of others whose behavior has been abnormal but has not brought them into conflict with the law. In the light of all available knowledge and with the scientific approach, the important human issue may then be dealt with: how to obviate or minimize repetition of such conflict, for the good of all concerned. 36 references. —*Author's abstract.*

80. *Psychology and Psychopathology of Arson, 1917–1955 (Zer Psychologie und Psychopathologie der Brandstiftung, 1917–1955).* W. DE BOOR. Fortschr. d. Neurol., Psychiat. *23*:367–378, Aug., 1955.

This is a review of the literature from 1917 to 1955 (inclusive) of the psychology and the psychoses observed in arsonists. References.

CLINICAL PSYCHIATRY

81. *Psychosis and Stuttering.* HENRY FREUND, Milwaukee, Wis. J. Nerv. & Ment. Dis. *122*:161–172, Aug., 1955.

Review of the literature reveals that the phenomenon of stuttering in the functional psychoses is generally overlooked. The first systematic study on the frequency of stutter-

ing was conducted by Barbara in 1946, who found stuttering in only 0.28 per cent in a state hospital of 7000 patients, as contrasted to the 1 per cent assumed to exist in the general population. In 149 ambulatory schizophrenic veterans, the author found 5 cases (3.25 per cent) of unquestionable stuttering, and, even in regressed schizophrenics, the number of stutterers seems larger than assumed. There seems to be a definite increase of stuttering in patients with some types of organic psychoses, especially in institutionalized epileptics. These findings speak against the formerly assumed rarity of stuttering among psychotics and also against the assumption that stuttering can serve as a defense against the outbreak of a psychosis.

The stuttering in a group of 27 schizophrenics, studied by the author, showed considerable persistency, though it was often concealed and difficult to detect. Stuttering can withstand electroshock, insulin coma treatment, and lobotomy and can become manifest during acute flare-ups of the psychosis after long periods of concealment. Another feature is that stuttering in the seriously ill apparently causes much less suffering, becoming a kind of incidental symptom. This was also found true in severe anxiety neurotics and psychopaths. Of special interest is an atypical (conversion hysterical) form of stuttering and a stutter-like speech (pseudostuttering) in schizophrenics which seem to overshadow in frequency genuine (Froeschels) stuttering. There was 1 case where this atypical kind of stuttering coincided with the onset of psychosis. The study of 2 cases by Barbara and 1 by the author of manic-depressive psychosis with stuttering showed definitive schizoid admixtures.

Parallel phenomena in stuttering and the psychoses, such as perceptual distortions, constriction of intellectual functioning, and distortion of self-evaluation, lack specificity since they are found in all emotionally, highly charged conditions, especially in phobias and panic states. More specific analogies are: (1) the similar role internal speech plays in the expectancy of stuttering, which may be of a hallucinatory-like intensity, and in the mechanism of auditory hallucinations; (2) the increased social anxiety; and (3) the possibly diminished threshold for confusion and thought dissociation in some stutterers and most schizophrenics when there is social stress.

The similarities between problems encountered in the study of stuttering and psychosomatic disturbances in psychotics were noted. The peculiar qualitative alterations and modifications of stuttering in psychotics are reminiscent of the modification of other neurotic phenomena in the psychoses. This study helps to contribute toward our knowledge of the relationship between the neuroses and the psychoses on a clinical descriptive level. 45 references. 3 tables.—*Author's abstract.*

82. *Anorexia Nervosa.* JAMES H. WALL, White Plains, N. Y. Bull. New York Acad. Med. *32*:116–126, Feb., 1956.

This study concerns the experience in management and treatment of 10 female patients with anorexia nervosa of sufficient severity to be treated in a mental hospital. The pertinent literature is reviewed with particular emphasis on the contributions of Sir William Gull, who carefully studied, understood, and named the condition. The differential diagnosis regarding Simmonds' disease, as presented by Farquharson and Hyland, is reviewed.

The 10 patients were between the ages of 16 and 38. They came of unstable families; all

of them showed a peculiar dependence upon the mother and at the same time a wish to hold the mother responsible for their condition. Most of them had been small infants and 2 had been premature; all had shown feeding difficulties and resisted changes to solids and a variety of foods. As a group they had moved from one level of adjustment to another with difficulty. This was particularly pronounced at the time of maturation, menstruation, and growth and rounding out of the body, and emotional stirrings of adolescence were rejected. Aversion to food accomplished a destroying of sex and life, kept them from growing up, and opposed the thriving of what apparently was interpreted by them as coarse, animal-like and disgusting. Only 2 had been admitted to the hospital when they were less than 20 years of age, and, of the 8 more than 20 years, only 3 were married; 2 of the 3 had children. All had been under treatment for many years. Their weight varied from 52 to 94 lb. Amenorrhea was present. All expressed an aversion to food, would hide it and throw it away, and would use every deception to appear to be holding their weight or to be gaining.

Although alert, restless, and overactive, there was a shallowness of affect. As to psychiatric diagnoses, these patients were said to have hysterias, obsessive-compulsive states, depressions, and schizophrenias in various clinics. The inability to relate to others, the lack of sustained drive, the flatness of affect, the withdrawal, and the delusional nature of their thinking about food and their mothers point to a diagnosis of simple schizophrenia.

The best treatment for patients with anorexia nervosa requires separation from their families. They must grow up again. They appreciate kind but firm attention. At times they must be tube fed to combat the emaciation. Ambulatory subshock insulin therapy is helpful. Electroshock therapy hastens progress. A varied hospital program of physiotherapy, occupational therapy, physical education, and social activities overcomes the withdrawal and asocial tendencies. With the rise in self-esteem, they become more responsive to psychotherapy. Reassurance and gentle but firm persuasion appear to work. They usually make limited adjustments, and allowance must be made for their limited powers of adjustment and maturing.

Of the 10 women, 7 have continued to do fairly well. All of them continue to be underweight and find it difficult to achieve a weight of more than 100 lb. 6 references.—*Author's abstract.*

83. *The Sedation Threshold, Manifest Anxiety, and Some Aspects of Ego Function.* CHARLES SHAGASS AND JAMES NAIMAN, Montreal, Canada. Arch. Neurol. & Psychiat. *74*:397–406, Oct., 1955.

The sedation threshold is an objective pharmacologic determination, which depends on electroencephalogram and speech changes produced by intravenously given amobarbital sodium. This procedure was developed to measure manifest anxiety, and its validity for this purpose was demonstrated in two studies of psychoneurotic patients. The main purpose of the present investigation was to determine whether the sedation threshold also measures manifest anxiety in nonpatient controls and in patients with certain psychotic disorders. The second purpose was to test two predictions, derived from the hypothesis that impairment of ego functions, such as reality contact, lowers the sedation threshold.

In 45 nonpatient control subjects there was a high positive correlation between the

sedation threshold and the number of symptoms of manifest anxiety elicited in a psychiatric interview. There was also a significant relationship between the threshold and the score on a self-administered symptom inventory (Saslow Screening Test). Psychotic patients included: 11 with organic psychoses, 11 acute schizophrenics, 22 with agitated depressions, and 34 chronic schizophrenics. In the psychotic group as a whole there was no statistically significant correlation between the sedation threshold and clinical appraisals of degree of tension or manifest anxiety. Among the chronic schizophrenics there was a significant positive correlation, which was smaller than that found in psychoneurotics or controls.

From the ego impairment hypothesis, it was predicted that the chronic schizophrenics would have higher thresholds than apparently equally tense acute schizophrenics or those with agitated depressions. It was also predicted that those with organic psychoses would have lower thresholds than any other subjects. The results confirmed both predictions.

It was concluded that the sedation threshold is positively correlated with degree of manifest anxiety and negatively correlated with degree of impairment of ego functioning. Since the ego impairment factor is important mainly in psychotics, it was concluded that the sedation threshold, as a measure of manifest anxiety, is most applicable to nonpsychotics. Various other clinical and research applications of the procedure were considered.

The phenomena related to the sedation threshold may at present be most readily understood in terms of reticular system activity, and recent evidence indicates that there is differential sensitivity to barbiturates in different components of this system. This differential sensitivity is probably related to the sedation threshold and, in turn, to the psychologic correlates of the threshold. 14 references. 4 figures. 2 tables.—*Author's abstract.*

GERIATRICS

84. *A Psychiatric Study of Attempted Suicide in Persons Over Sixty Years of Age.* PATRICIA O'NEIL, ELI ROBINS, AND EDWIN H. SCHMIDT, St. Louis, Mo. A.M.A. Arch. Neurol. & Psychiat. *75*:275–284, March, 1956.

In a study of 109 patients who had attempted suicide, 19 were more than 60 years. All 109 patients were examined and interviewed immediately after making a suicide attempt. The data used in this study are based on the interview with these 109 patients.

The most noteworthy finding was that every patient in the older age group was found to be suffering from a definite psychiatric disease. These diseases were: (1) chronic brain syndrome (5 patients); (2) manic-depressive depression (9 patients); (3) acute confusional states (3 patients); and (4) chronic alcoholism (2 patients). It was also striking that 89 per cent of these patients in the older age group had a psychotic disease and that, of the 15 or so major diagnostic categories in psychiatry, only four categories were represented in this older group of patients.

Comparison between the younger and older groups revealed the following important differences: (1) Suicide attempts in the older group were more often serious than in the younger group. (2) Potentially life-disturbing situations occurred more frequently in the younger than in the older group (the only exception was in the case of a serious medical or

surgical illness where illness occurred more frequently in the older group). (3) While there were no undiagnosed patients in the older age group, it was not possible to make a diagnosis in 23 per cent of the younger group. (4) Patients in the younger group were classified in 10 different diagnostic categories, while those in the older group were classified in only four diagnostic groups. (5) While 89 per cent of the older age group were psychotic, only 23 per cent of the younger patients were psychotic.

The authors feel that all elderly patients who attempt suicide should be hospitalized for treatment of their underlying psychiatric illness and for prevention of a further attempt. Since most older patients suffer from a treatable (psychotic depression) or reversible (acute brain syndrome) disease, they can be rehabilitated and returned to society as useful citizens. 10 references. 4 tables.—*Author's abstract.*

85. *Sleep and Sleep Disturbance in Geriatric Psychiatry.* RAPHAEL GINZBERG, Tomah, Wis. J. Am. Geriatrics Soc. *3*:493–511, July, 1955.

This survey is based on two studies of the sleeping habits of 351 psychotic and nonpsychotic elderly individuals. It includes 70 nonpsychotic or mildly psychotic Iowa county-home residents, with a mean age of 74.8 years, and 281 neuropsychiatric patients of the Veterans Administration Hospital, Tomah, Wisconsin, with a mean age of 62.3 years. Material was evaluated clinically and statistically. The results are: (1) Insomnia is more frequent in less deteriorated and/or less or nonpsychotic elderly persons. (2) No statistical significance was found in correlating insomnia with age factor, general arteriosclerosis, blood pressure, occupation, or length of hospitalization. (3) Of statistical significance were correlations of insomnia with some psychologic and environmental factors and diagnosis, stressing that affective components primarily account for sleeplessness. (4) Major sleep disturbances requiring treatment with hypnotic drugs comprise roughly 5 per cent of patient-days in the V. A. Hospital group. It was concluded that insomnia is not a major problem in psychotic or nonpsychotic elderly persons who live in a favorable environment.

In all cases of insomnia, regardless of the presence or absence of organic brain damage, a psychologic approach is indicated. Concurrent with any somatic treatment deemed necessary, attention should be directed primarily toward the elderly individual's adaptational difficulties and toward detection of destructive factors in his environment. 66 references. 16 tables.—*Author's abstract.*

86. *Chlorpromazine in the Management of the Institutionalized Aged Psychiatric Patient with Chronic Brain Syndrome.* ALBERT A. KURLAND, Baltimore, Md. Dis. Nerv. System. *16*:366–369, Dec., 1955.

A study was conducted on 52 patients between the ages of 60 and 90 years, all of whom exhibited, to varying degrees, the basic syndrome of chronic brain disorder. This syndrome was associated with psychiatric, neurotic, or behavioral disturbances of such magnitude that the patient could no longer be managed outside of a psychiatric hospital. Twenty-six of the 52 patients served as a control group. The control group was treated by standard methods, including electroshock, and did not receive chlorpromazine. The other 26 patients

were treated with chlorpromazine alone for periods varying from 15 to 252 days. The daily dose, adjusted to each patient individually, varied from 50 to 400 mg. All of these patients had failed to respond to previous therapy.

Of the 26 patients treated with chlorpromazine, 6 showed marked improvement, 6 were moderately improved, 5 showed minimal improvement, and 3 showed no change; 1 patient seemed to become worse. Five deaths occurred in this group; 3 were due to cardiac failure and 2 to generalized arteriosclerosis. None was directly attributable to chlorpromazine. Five patients, whose medication was withdrawn after they responded to treatment, regressed and were placed on a second course of chlorpromazine. All 5 responded well to the second course, and none has again shown signs of regression, even though chlorpromazine was withdrawn the second time in 3 cases. Four patients were discharged: One of them stopped taking the medication on leaving the hospital and was readmitted two months later in a state of regression; 2 were continued on the medication after leaving the hospital and have been able to remain at home; and 1 stopped taking chlorpromazine while in the hospital and was subsequently given 10 electroshock treatments following which she showed additional improvement and was discharged.

Of the 26 patients in the control group, 1 showed marked improvement, 1 had minimal improvement, and 18 showed no improvement. Six patients in this group died during the course of the study. Side effects were noted in 7 patients: jaundice in 3, rash in 3, and parkinsonian-like reactions in 1. All side effects were readily controlled. The results of this study indicate that chlorpromazine is of value for both the treatment and management of institutionalized, aged patients with chronic brain syndrome. It is the author's impression that the degree of response seems to be related inversely to the degree of organic brain damage. The greater the evidence of brain damage, the less the response. 7 references.—*Author's abstract.*

HEREDITY, EUGENICS, AND CONSTITUTION

87. *Genetic Aspects of Preadolescent Schizophrenia.* FRANZ J. KALLMANN AND BERNARD ROTH, New York, N. Y. Am. J. Psychiat. *112*:599–606, Feb., 1956.

Statistical data on the family backgrounds of two samples of preadolescent schizophrenia cases (52 twins and 50 singletons younger than age 15 years) are compared with previously collected family data on twins with the more common adult forms of schizophrenia. This comparison reveals neither statistically significant differences between preadolescent and adult groups with schizophrenia, with respect to the schizophrenia rates for the parents (12.5 and 9.3 per cent) and sibs (12.2 per cent and 14.3 per cent), nor any difference between the schizophrenia rates for fathers and mothers. However, there is an increased number of early schizophrenia cases among the co-twins and sibs of early cases, as well as a consistent excess of males in the preadolescent group.

Dizygotic and monozygotic co-twins of schizophrenic twin index cases differ as much in regard to preadolescent schizophrenia (17.1 and 70.6 per cent) as they do with respect to adult schizophrenia (14.7 and 85.8 per cent). The psychoses in the co-twins of early cases

occur sometimes before and sometimes after adolescence. This finding indicates that pre-adolescent and adult forms are differentiated by a number of secondary factors influencing constitutional resistance rather than by different gene-specific deficiency states.

That there is no simple correlation between the inadequacy of the parental home and the severe maladjustment in children is demonstrated by the fact that the homes of 71.4 per cent of all sibs and dizygotic co-twins of early schizophrenics, and the homes of 82 per cent of those diagnosed as schizoid or schizophrenic, are classifiable as inadequate. In evaluating this finding, it is to be noted, however, that, of all the sibs and two egg co-twins classified as normal, 64.8 per cent come from an inadequate home, identified with the development of schizophrenic phenomena in the index cases. 19 references. 7 tables.—*Author's abstract.*

PSYCHIATRY OF CHILDHOOD

88. *Introduction to the Symposium on Developmental Disorders in Children—Their Mechanisms and Management.* I. NEWTON KUGELMASS, New York, N. Y. Internat. Rec. Med. & G.P.C. *169*:313–314, June, 1956.

The mechanism of developmental disorders in children is viewed from the standpoint of intrauterine patterns of human development. Most structures are formed and then vanish without apparent function; some built up in one place migrate to a different site; and even the formation of vital organs depends on the meeting and fusion of processes emanating from widely separated points. The first trimester of pregnancy is therefore the period of greatest susceptibility to developmental anomalies. The study of these disorders calls for the recognition not only of the casual relationship between the pathogenic genes and the end stage but also of the entire dynamic process during the prenatal and postnatal developmental periods in order to correct congenital defects, maintain superior nutrition, provide personalized psychologic care, integrate personality factors, and administer prophylactic and therapeutic measures. Pediatric supervision thus entails an assessment of developmental health in terms of rate of maturation of the mental, physical, emotional, and social development, as well as of physical health in terms of current constitutional status. Treatment may alleviate or cure, but only complete understanding can abolish developmental disorders. 1 table.—*Author's abstract.*

89. *Psychochemotherapy of Mental Deficiency in Children.* I. NEWTON KUGELMASS, New York, N. Y. Internat. Rec. Med. & G.P.C. *169*:323–338, June, 1956.

The mechanism of psychochemotherapeutic action is formulated on the basis of current experimental studies. Chlorpromazine blocks the arousal reaction and reserpine arouses the activity system, but both depress the hypothalamic center controlling basal metabolism, blood pressure, and the wake-sleep cycle. Each functions specifically without synergism. Ten such psychochemotherapeutic compounds were evaluated in 240 mentally retarded children manifesting 25 single symptoms, comprising six groups of problems studied in private and institutional practice for a five year period. Some of the quantitative com-

parisons were amenable to determinations of means, standard deviations, and standard errors; in large numbers differences greater than three times the standard error were significant, but in small numbers this rule maintained only when the number of cases exceeded 15.

The most effective results were observed in young aments with 8 specific predominant symptoms and the least effective in those with 17 of the 25 common manifestations studied. The quick-acting compounds chlorpromazine and meprobamate produce more favorable results than the slower-acting reserpine and methylphenidylacetate hydrochloride. Hexobarbital sodium is the only barbiturate that relaxes rather than stimulates aments. These psychochemotherapeutic agents were also compared with established therapeutic agents for intellectual impairment, motor disturbances, body manipulations, alimentary disturbances, elimination disorders, and sleep disturbances. Psychochemotherapeutic compounds suppress overt manifestations in the retarded child without eliminating underlying pathology, but the original symptoms are completely reversed upon withdrawal of therapy. 38 references. 1 figure.—*Author's abstract.*

PSYCHIATRY AND GENERAL MEDICINE

90. *The Use of Azacyclonol and Pipradrol in General Practice.* THOMAS G. ALLIN, JR. AND RAYMOND C. POGGE, Cincinnati, Ohio. Internat. Rec. Med. & G.P.C. *169*:222–230. April, 1956.

Pipradrol is a new antidepressant suitable for oral administration. The tablets contain 1 mg., and the daily dose in children varies from 1 to 3 mg./day. In adults, the usual dose is 6 mg./day, although many patients respond favorably to 3 mg., and in geriatric patients it is 2 mg. given early in the day.

Indications are emotional fatigue and depression, as seen in geriatric patients, in obstetric patients, in obese patients, in chronically ill patients, in alcoholics, and in those who are depressed or sedated as a result of administration of drugs.

Although azacyclonol is chemically similar to pipradrol, it is indicated in the symptomatic treatment of hallucinations and delusions associated with schizophrenia, alcoholism, and the postoperative state. Despite the use of a wide variety of doses by various investigators, it appears that a 20 mg. dose orally three times daily may be adequate for maintenance therapy. Azacyclonol can be administered parenterally early in the course of treatment, in which case it is given intravenously in doses of 100 mg. every eight hours. Concurrent administration of intravenous and oral azacyclonol is frequently helpful early in the course of treatment of schizophrenia. In patients in whom hallucinations are associated with alcoholism and the postoperative period, it is not always necessary to employ the oral maintenance dose. Many patients of this type respond favorably to a relatively small number of intravenous injections. 46 references. 2 figures.—*Author's abstract.*

For Reference

91. *Kraepelin and Modern Psychiatry (Kraepelin und die gegenwärtige Psychiatrie).* KURT SCHNEIDER, Heidelberg, Germany. Fortschr. d. Neurol., Psychiat. *24*:1–7, Jan., 1956.

PSYCHIATRIC NURSING, SOCIAL WORK, AND MENTAL HYGIENE

92. *Nursing in Psychiatric Hospitals.* KATHLEEN BLACK, New York, N. Y. Ment. Hyg. *39*:533–544, Oct., 1955.

As improved programs of psychiatric treatment have been instituted, nurses have increased in numbers in both public and private mental hospitals. More and better prepared nurses are still needed, however. Schools of nursing have attempted to keep pace with developments in the field, and have provided for a basic learning experience in psychiatric nursing for their students. Unfortunately, many students have been sent to poorly developed clinical settings, and have thus failed to develop a taste for later employment in the specialty.

A re-evaluation of both educational and employment practices in psychiatric nursing is essential. Many educational programs draw their subject matter from descriptive psychiatry exclusively. Others stress the participation of the nurse in a program of individual psychotherapy, whereas the employed nurse finds this type of treatment provided for only a small fraction of the patients. There is a lack of agreement among nurses and psychiatrists about the nature of the relationships that should be developed between nurses and patients.

There are very few beginning (or general duty) positions for nurses in psychiatric facilities, although this is the position for which the nurse is prepared in the basic professional program. In most mental hospitals, there is a tendency to place the few nurses who are employed in positions of immediate and heavy responsibility without adequate nursing supervision. The supervisor should be a person of high personal and professional attainments who is capable of inspiring her supervisees as well as giving them competent guidance.

The psychiatric aide is an indispensable worker in the mental hospital community. In view of the overwhelming need, it would seem to be desirable to prepare a group of workers, in less time and at less cost than through general and professional nursing education, to administer some of the interpersonal type of nursing care required by psychiatric patients. The two national nursing organizations are working toward this and other phases of psychiatric nursing education and service.—*Author's abstract.*

93. *The Community Stake in the Mental Health Program.* JACK R. EWALT, Boston, Mass. Am. J. Psychiat. *112*:248–251, Oct., 1955.

A brief review of 100 year old news items shows that tensions are not new in the world and are not apt to disappear. Therefore, the emphasis of the goal of a mental health program should be on the development of a population with character traits strong enough to adjust to the tensions and demands of the world. The author stresses the responsibility of the community's citizens in achieving this goal.

A mental health program should have facilities for detecting maladjustments or emotional crises so that corrective measures can be instituted before symptoms develop. Consultation and support should be available for teachers and other significant persons in the community who deal with people who have emotional problems. Services for the early treatment of mental or emotional illness should be offered, as well as hospital care when it is needed.

The problems of the mental hospitals in America are reviewed. The costs for the care of mental patients, while staggering in total, represent only a few dollars per day for each patient treated. To treat all patients at $18.00 per day, the cost for the care of a patient in many general hospitals, would be about 4 million dollars a year. The shortage of mental health personnel, particularly physicians, psychologists, psychiatric social workers, occupational therapists, and nurses, is acute. The citizens of the community must take an active role in seeing that adequate training and adequate salary levels are provided so that these services will be increased. It is felt that such constructive activity would contribute to the mental health of the community.—*Author's abstract.*

PSYCHOANALYSIS

94. *A Current Psychoanalytic Concept of God.* JOSEPHINE H. ROSS, New York, N. Y. Internat. Rec. Med. & G. P. C. *168*:760–767, Dec., 1955.

Beginning with an allusion to Freud's *Future of an Illusion*, this paper points out that an attempt has been made on the part of some psychoanalysts to carry on from the point at which Freud left off in his attempt to work through the meaning of the concepts of religion and God. Among these have been Jung, Rank, Reik, Horney, and Fromm. Of these, Fromm is currently probably making the greatest inclusive advances. Unlike Fromm, who has chiefly discussed the relation of psychoanalysis and religion, the writer points out new concepts of God that are currently evolving from the goals of psychoanalysis. It is her thesis that God is what each person makes Him out of his own individual needs. A well-analyzed person no longer has a need for a father-god but recognizes and delights in a recognition of a God conceived as his own constructive potential and from this can have faith in the constructive force in all human beings. He then fears neither himself nor others, life nor death, for he sees that his love of life and faith in himself will have an effect on other lives in a vast continuum of human existence.

The readiness of the individual to accept a belief in a father-god is discussed and explained, as well as the role of the analyst as God in the transference phenomenon. Case material is utilized for illustrative purposes. 19 references.—*Author's abstract.*

PSYCHOLOGIC METHODS

95. *The Figure-Ground Syndrome in the Brain-Injured Child.* HEINZ WERNER AND ALASTAIR WEIR, Worcester, Mass. Internat. Rec. Med. & G.P.C. *169*:362–367, June, 1956.

The figure-ground syndrome is characterized by a leveling of normally distinct figure and ground processes. This disturbance has been widely investigated by Werner, Strauss, and their collaborators in normal children, endogenous mentally defective children, and exogenous mentally defective children. Throughout, the exogenous children were found to

be much more susceptible to background interference, while the performance of the endogenous children was comparable to that of normal children of the same mental age. In the field of perception, this effect was demonstrated by experiments utilizing the Rorschach test, tachistoscopically presented figure-ground pictures, two forms of the Werner-Strauss Marble-Board Test, and an investigation of the tactual-motor field, in the area of memory, by using dot pattern and word list material; and in conceptual thinking, by means of "Picture-Object" and "Picture-Story" tests. 11 references. 4 figures.—*Author's abstract.*

96. *The Distribution According to Age of a Psychologic Measure Dependent upon Organic Brain Functions.* RALPH M. REITAN, Indianapolis, Ind. J. Gerontol. *10*:338–340, July, 1955.

The psychologic tests developed by Halstead were administered to a group of 194 persons with unequivocal evidence of brain damage and to a group of 133 persons with no neurologic or anamnestic evidence of brain damage. Highly significant intergroup differences were obtained, substantiating previous findings. The Halstead impairment index, particularly, was found to be highly sensitive to the organic condition of the brain. The second part of the study compared the distribution of the impairment index along the age continuum in the two groups. The groups were divided into five year intervals from age 15 to 65 years, and mean curves for the impairment index were plotted. Significant impairment was present throughout the age distribution for the brain-damaged group, and the impairment index in this group was relatively uninfluenced by age. The group without neurologic or anamnestic evidence of brain disease or damage, however, showed a distinct relation between age and impairment index. The correlation of .61 was contributed largely by individuals 45 years of age and older. These results suggest that the impairment index may be a valid indicator of rather subtle changes in brain function that sometimes occur in the middle and older age ranges. 3 references. 1 figure. 1 table.—*Author's abstract.*

PSYCHOPATHOLOGY

97. *Thinking Disturbances in Delirium.* MAX LEVIN, New York, N. Y. A.M.A. Arch. Neurol. & Psychiat. *75*:62–66, Jan., 1956.

Patients in delirium show some of the association disturbances that Bleuler studied in schizophrenia; they show defects in their thinking. To give an example, a patient said, "This is the northeastern part of the city." When he was asked how he knew this, he replied that he could tell from the angle of the sunbeams coming in the window. This is poor logic, for the angle of the sunbeams shows the direction the house faces and not the section of the city.

Delirious patients disoriented for person and unable to name your vocation correctly may nevertheless spontaneously address you as "doctor," as when they say, "Good morning, doctor." This is comparable to a phenomenon in aphasia, when a patient who cannot name an object on command will name it spontaneously, as when he asks to borrow your pencil.

This type of selective loss of function is understandable in the light of John Hughlings Jackson's views of cerebral function. 7 references.—*Author's abstract.*

98. *Demarcation of the Concept of Projection (Deslinde del concepto de proyeccion).* S. M. LUZA, Lima, Peru. Rev. de psicol. gen. y aplicada *10*:291–301, April-June, 1955.

Projection, as a psychologic phenomenon, participates in the individual's history and in his relation to the environment. It is related to the peculiarities of the various periods of the individual's life and with the fluctuations of the consciousness of the ego. Projection is characteristic of certain personalities and manifests itself through a native incapacity to adapt to circumstances. It is manifested in the psychoneuroses and the psychoses; in the former it is used as a mechanism to evade responsibility and in the latter as a result of organic modification unrelated to unconscious content.

99. *The Need to Believe—Persistent Religious Behavior in Non-Believers.* MORTIMER OSTOW, New York, N. Y. Internat. Rec. Med. & G. P. C. *168*:798–802, Dec., 1955.

Some individuals who do not subscribe to and participate in organized religion disclose in psychoanalysis residual fragments of religious attitudes and practices. It is inferred that unconscious wishes and fantasies, persisting from childhood and directed toward the childhood images of the parents, enforce attitudes and acts having a religious form, even though the conventional religious objects, the deity, and the creed have been repudiated. The disavowal of religion does not cancel the need to believe. Religion mobilizes individuals by means of this need to believe into an organization that serves a socially uniting rather than a disintegrating function. Quasi-religious beliefs, on the other hand, because of their idiosyncratic nature, serve a function within the psychic economy but play no role in social regulation.—*Author's abstract.*

TREATMENT

b. Drug Therapies

100. *Studies in Pharmacological Psychotherapy.* THEODORE ROTHMAN AND KEITH SWARD, Beverly Hills, Calif. A.M.A. Arch. Neurol. & Psychiat. *75*:95–105, Jan., 1956.

The authors report on the use of pharmacologic psychotherapy with 16 psychiatric patients, all of whom had previously undergone psychoanalysis unsuccessfully for periods of six months to three years. All of the patients, who had personality disorders or psychoneuroses, were rigid people who were moderately or severely impaired in occupational or social adjustment. In trial psychotherapy with the authors, they experienced, as they had previously, an inability to form close interpersonal relationships without disabling anxiety, rising psychic tension, and resultant difficulties in meaningful communication. In an effort to overcome their inaccessibility, the authors began to use intravenous thiopental sodium

and methamphetamine hydrochloride. In combination, the drugs decreased psychic tension and hypervigilance, induced alertness, promoted spontaneity and well-being, enhanced rapport and communication, increased drive and responsiveness in communication, and diminished autonomic nervous system overflow, thus reducing the patients' insulation to psychotherapy.

Before treatments were begun, patients were prepared psychologically. At the time of treatment, 3 to 7 ml. of a 2.5 solution of thiopental sodium was injected intravenously, followed through the same needle by 5 to 15 mg. of methamphetamine hydrochloride. The patients had 50 minute interviews, once or twice weekly. At first, therapeutic hours without use of drugs were occasionally interspersed with "drug interviews;" later, an increasing proportion of interviews were carried on without drugs, until they could be dispensed with entirely. Once the optimal psychophysiologic state was induced, the psychodynamic forces usually associated with successful psychotherapy came into play. Ego defenses were lowered, and communication and participation in therapy were enhanced; the patients showed increased capacity for integration, for breaking through psychic paralysis, and for growing.

On this regimen, 3 of these refractory patients showed no improvement, 7 slight improvement, 5 moderate improvement, and 1 considerable improvement. Length of treatment extended from six months to four years. While improvement was partial and undramatic, it was still surprising in a series of patients whose personality difficulties included a large admixture of moderate to severe obsessive-compulsive states as either the primary or secondary disorder. Apparently psychotherapy and the drugs, acting together, accomplished what neither could have effected alone. Furthermore, the 13 patients who improved seem to be holding their gains. The authors conclude that pharmacologic psychotherapy shows promise of becoming a method of choice for the treatment of refractory, moderate to severe psychoneuroses and personality disorders. 52 references. 3 figures. 3 tables.—*Author's abstract.*

101. *A Comparison of Chlorpromazine and Reserpine in Chronic Psychosis.* B. KOVITZ, J. T. CARTER, AND W. P. ADDISON, Columbus, Ohio. Arch. Neurol. & Psychiat. *74*:467–471, Nov., 1955.

One hundred and fifty chronic psychotic patients, chiefly schizophrenics, were divided into three groups. One group was treated with chlorpromazine for six weeks, placebos for four weeks, and reserpine for six weeks. The second group was similarly treated with reserpine followed by chlorpromazine. The third group received only placebos. The maximum dose of reserpine was 4 mg. daily; the maximum dose of chlorpromazine was 400 mg. daily. Clinical improvement occurred in 53 per cent of cases receiving reserpine, in 58 per cent of cases receiving chlorpromazine, and in 24 per cent of cases receiving placebos. The placebo group required three times as much electroconvulsive therapy. Eleven of the group that received chlorpromazine and reserpine could be released from the hospital; 1 patient of the placebo group was released. Patients on chlorpromazine showed a slight, but significant, increase in intelligence test scores, presumably because of less anxiety. Both drugs tended to decrease muscle tension artefact in the electroencephalogram. Drug rashes required discontinuing chlorpromazine in 5 per cent of the cases. Reserpine took longer to produce improvement

in the doses used. Both drugs produced symptomatic improvement in overt behavior and emotional expression more readily and reliably than in psychotic thinking. Depression was not relieved. Best results appeared in patients with evidence of anxious or hostile tension and persistent efforts to maintain self-esteem. Both drugs appeared to be of particular value for the chronic but nondeteriorating schizophrenic group. 5 tables.—*Author's abstract.*

c. Psychotherapy

102. *Personality Needs, Religion, and Psychotherapy.* ALEXANDER A. SCHNEIDERS, New York, N. Y. Internat. Rec. Med. & G. P. C. *168*:790–792, Dec., 1955.

There is today an obvious interest in the relation between religion and healing. Psychologists, psychiatrists, and religious persons are repeatedly pointing out this relationship in various publications. This is true of both Catholic and non-Catholic sources, all of which emphasize the therapeutic value of religious beliefs and practices.

Despite this relationship, however, it is nevertheless true that many devoutly religious people are not mentally healthy, nor is sanctity a guarantee of mental health or stability. Also, religion may be not only inefficacious but actually disruptive of mental health. Thus, many persons are deeply troubled by the demands that religion makes on them. The struggle against sin, confession, and the demands of morality may lead to considerable guilt, inadequacy, and inferiority. Apart from all this, we may note also that there are many nonreligious people who seem to be quite well adjusted, so that there is not an essential relation between religion and mental health. These observations require a most careful evaluation of the relationship in question. We cannot assume that religion in and of itself will promote or guarantee mental health. Religion is salutary to mental health and to therapy only when it is able to furnish perdurable values that promote personal growth and integration. When religious experiences are basic and pervasive and religious practices reduce conflicts and frustrations, religion becomes a powerful psychologic tool for the individual as well as for the therapist. Admittedly, religion is admirably suited to the gratification of basic needs, such as security and personal worth, and this fact can be exploited to advantage in the therapeutic situation.—*Author's abstract.*

103. *Special Techniques in Brief Psychotherapy.* HARRY L. MAC KINNON AND ARNOLD ALLEN, Dayton, Ohio. Dis. Nerv. System *16*:277–283, Sept., 1955.

We have brought together for wider applications some of the special techniques in dynamically oriented brief psychotherapy frequently referred to and often written about, but usually with somewhat limited application. These techniques are discussed here with the goal of restoring the inner equilibrium of patients on a more permanent basis. References are made to some of the pertinent literature, particularly with regard to special techniques in phases of intensive therapy, psychosomatic conditions, and borderline or psychotic cases. There are numerous patients in whom brief psychotherapy is the treatment of choice, such as, patients with acute cases in whom something immediate is to be accomplished, the fixed neurotic, the borderline psychotic, and the patients with psychosomatic

illnesses. Again, at times there are realistic factors, such as age, finances, physical conditions, and limited psychiatric facilities, that would contraindicate intensive psychotherapy, leaving brief psychotherapy as the most effective approach.

The important techniques in brief psychotherapy are divided into three main categories. The first includes situations that call for a restoration of old defenses protective against psychosomatic conditions, psychoses, more severe neurotic disturbances, surrender to physical conditions, and ego breakdowns. The second special technique consists of satisfying the neurotic needs of the patient. Possibilities that the therapist may initiate with this technique are giving the patient a feeling of controlling, giving the patient an independent feeling, satisfying the masochistic needs of the patient, satisfying the need for combativeness, satisfying the needs for voyeurism and exhibitionism, satisfying the need to project omnipotence, satisfying the need for complete acceptance, satisfying the need to be protected, catering to narcissistic needs, and satisfying the need to deny dependence. The therapist may also function in a passive manner by allowing the patient to act out in the treatment situation, allowing ambivalence to develop, allowing hostility to come out in caricature of what is thought to be expected, allowing competitiveness, and allowing masked improvement. The third technique discussed consists of working therapeutically with the patient's family. Some examples of these techniques of brief psychotherapy have been used by way of illustration. The main emphasis has been largely on their value as ways of helping the patient to arrive at a better degree of equilibrium rather than on their use in the more intensive therapies. 22 references.—*Author's abstract.*

d. The "Shock" Therapies

104. *Technique for the Modification of Electroshock with Succinylcholine.* H. JEROME RIETMAN AND ENRIQUE DELGADO, Hartford, Conn. Dis. Nerv. System *16*:237–242, Aug., 1955.

A method for modifying electroshock treatments with succinylcholine chloride, a short-acting muscle relaxant, is described. These treatments are given to fasting patients premedicated with 0.8 mg. of atropine sulfate. A light plane of anesthesia is produced by intravenous pentothal sodium in a 2.5 per cent solution, followed by an injection of succinylcholine. Approximately 20 mg. of the relaxant per 50 pounds of body weight is used, a dose that eliminates the muscular components of the electrically induced seizure except for mild clonic contractions of the orbicularis oris and oculi muscles. Before and after the markedly subdued seizure, artificial respiration with pure oxygen is supplied, using a tight fitting face mask and manipulating the rebreathing bag until spontaneous respiration resumes. During the postseizure phase, mouth secretions are routinely removed with a suction apparatus. Total time from start to finish of the treatment usually varies from 6 to 10 minutes.

A series of 3316 succinylcholine-modified electroconvulsive treatments in 291 patients over a two year period was compared with a series of 1975 unmodified treatments in 167 patients over the same period. There was no difference in therapeutic effectiveness. However, the modified procedure reduced the usual complications of electroshock therapy

almost to nonexistence. Only one minor fracture occurred, whereas in the smaller, unmodified group, fractures of the thoracic vertebrae occurred in 4 patients, and a ligament tear with minute cortical fracture of the left humoral neck in another. Complaints of pain dictating roentgen-ray examination were almost four times more frequent in the unmodified treatment series. Pulmonary and cardiac complications were not encountered in the modified treatments, although patients with severe heart disease were treated. The modified method offered a reasonably safe opportunity to treat older patients and patients with serious physical disorders for whom such therapy was previously contraindicated. 7 references. 1 table.—*Author's abstract.*

105. *Clinical Results of Selective Leukotomy Based on Intracerebral Electrography.* MAGNUS C. PETERSEN, HENRY W. DODGE, JR., CARL W. SEM-JACOBSEN, JORGE A. LAZARTE, AND COLIN B. HOLMAN, Rochester, Minn. J. A. M. A. *159*:774-775, Oct. 22, 1955.

A study of the electric potentials encountered in the depth of the frontal lobe in man was commenced in 1949. At first, recordings were made in the operating room on patients undergoing prefrontal leukotomy. In 1952, with the introduction of flexible microelectrodes that could be left in position indefinitely, it became possible to study the patient in the laboratory under controlled conditions. The prolonged period of study overcame or minimized the effects of surgical trauma and anesthesia. Furthermore, the electric potential in the depth of the brain could be recorded while the patient was in various physiologic states or in states induced experimentally.

Invariably slow waves of 2 to 4 cycles/second were recorded from a circumscribed area in the ventromedian quadrant of the frontal lobe in the plane of the coronal suture. It was thought that this area might mediate impulses causing or enhancing abnormal mental states. Therefore, the prefrontal leukotomy was limited to this area.

Since July 12, 1954, this selective type of leukotomy has been performed on 63 mentally ill patients varying in age from 16 to 72 years, the average age being 38.1 years. The duration of the mental illness varied from 1.5 to 36 years, the average being 9.4 years. The length of continuous hospitalization varied from 3 months to 35 years, the average being 5.5 years.

On Nov. 12, 1954, when this evaluation was made, 14 of the patients had adjusted socially, 37 were much improved, 8 were slightly improved, 1 was unimproved, and 3 were dead. Sixteen of the group had been dismissed from the hospital. Four of the patients were diagnosed as having involutional psychoses, 53 schizophrenia, 3 mental deficiency, and 3 organic psychoses.

The clinical results from this selective leukotomy are better and the undesirable aftereffects fewer than after the more extensive types of prefrontal leukotomy. 6 references. 1 table.—*Author's abstract.*

neurology

CLINICAL NEUROLOGY

106. *Hereditary (Familial) Spastic Paraplegia.* GABRIEL A. SCHWARZ AND CHAN-NAO LIU, Philadelphia, Pa. A.M.A. Arch. Neurol. & Psychiat. *75*:144–162, Feb., 1956.

The patient was a member of a family reported on previously. In this family a progressive spastic weakness of both lower extremities had afflicted numerous individuals over six generations. The patient began to have trouble walking when he was 18 years of age. He developed a progressive weakness and spasticity of the muscles of his lower extremities which eventually resulted in his being invalided by a contractured, hyperreflexic, spastic paraplegia in flexion. He also showed some increased reflexes and bilateral Hoffmann's signs in his upper extremities. He died at the age of 57 years from an infection unrelated to this illness.

The following significant abnormalities were noted in the microscopic study of this patient's spinal cord: (1) demyelinization and loss of axis cylinders of both crossed corticospinal tracts evident below the midcervical level and most extensive in the thoracic levels; (2) demyelinization and loss of axis cylinders of both dorsal spinocerebellar tracts of Flechsig traceable into the medulla oblongata; (3) demyelinization and loss of axis cylinders of the medial portions of the columns of Goll upward from the lowest thoracic level, most marked in the upper cervical level, and traceable to the gracile nuclei in the medulla oblongata; and (4) loss of neurons in the dorsal nuclei of Clarke.

The microscopic study of the medulla oblongata revealed that one pyramid just above the decussation had an area of 5.87 sq. mm. and that the calculated total number of nerve fibers in this pyramid was 376,055. The diameters of 37,581 nerve fibers were measured, and the authors found that 89 per cent measured 1 to 4 microns in diameter, 8.8 per cent measured 5 to 10, and only 2.2 per cent measured above 11 microns.

The microscopic study of the cerebral hemispheres showed no significant changes in the cortical neurons of the motor and premotor regions. Calculations of the number of Betz' cells in one (left) motor cortex gave the figure of 23,652.

The changes in the fiber pathways and nuclei of the spinal cord were like the changes reported by such other investigators as Strümpell, Newmark, Jakob, and Kahlstorf. The authors found the pyramids to be smaller than normal (Duncan, in 1940, found the area to be 8.16 to 13.7 sq. mm.). We also found fewer nerve fibers in the pyramid than normally (Lassek, in 1942, found 625,700 myelinated nerve fibers in one pyramid of a 20 year old colored man), and we found fewer Betz' cells in one motor cortex than are normally there (Lassek counted 34,000 Betz' cells in one cerebral hemisphere). The significance of these losses is uncertain. Further quantitative observations of similar cases would seem to be urgently indicated before any worthwhile explanation of these findings can be offered. It is still our feeling that the major pathologic focus is in the thoracic portion of the spinal cord in cases of hereditary spastic paraplegia. It is felt that the changes observed in the medulla

and motor portion of the cerebral cortex in the authors' patient were not contradictory to this theoretic localization. 42 references. 4 figures.—*Author's abstract.*

107. *Role of Non-Directive Play Therapy as a Technic of Psychotherapy in Cerebral Palsy.* EDWARD J. LORENZE AND RALPH CANCRO, White Plains, N. Y. Arch. Phys. Med. 36: 523–529, Aug., 1955.

The successful management of the child with cerebral palsy throughout the developmental years has as its goal of "habilitation" the evolution of an adult who has achieved his maximal potentialities both in function and adjustment. With this goal in mind, the Psychology Department of The Burke Foundation Cerebral Palsy Clinic has attempted to integrate, with other habilitation disciplines, a program of play psychotherapy.

A group of 15 children with cerebral palsy was placed on individual play psychotherapy. The frequency of treatment for the 10 reported on (the remaining 5 patients had had too few sessions at the time of preparation of the article) varied from one to two hours weekly, and total sessions per patient ranged from 15 to 32 hours.

These 10 children were referred because of behavior problems of at least one year in duration at home, clinic, or school. The problems were manifested by temper tantrums; attempts at physically harming other children; uncontrolled hyperkinetic activity; lack of attention and cooperation with teachers, parents, and therapists; and withdrawal, with poor socialization patterns. The other associated cause for referral was absent or retarded speech, which was considered, at least partially, a result of emotional maladjustment or immaturity.

On postpsychotherapy evaluation of these patients by the clinic staff in terms of the original reasons for referral, there was definite improvement in behavior or speech in 8 children and no significant change in 2 children. While no control study was reported, it was the clinical impression of the authors that the children with emotional disturbances who had been on play therapy made greater improvement in behavior, speech, and cooperation with therapists than similar children who did not have the benefit of psychotherapy.

It is the experience of the authors that emotional problems are found in sufficient frequency among children with cerebral palsy to warrant the inclusion of psychologic services as an integral part of the therapeutic programs in cerebral palsy clinics. 3 references. 2 tables.—*Author's abstract.*

108. *Psychological Problems of Patients with Myasthenia Gravis.* MARIA BROLLEY AND MARC H. HOLLENDER, Chicago, Ill. J. Nerv. & Ment. Dis. *122*:178–184, Aug., 1955.

This study represents an attempt to understand the adjustment problems and emotional difficulties experienced by patients suffering from myasthenia gravis. Interest was stimulated by an adolescent girl with this illness, who was referred for psychotherapy and was seen for 16 months. Twelve additional patients were seen for detailed anamnestic interviews. All the patients had been informed of the diagnosis and had been presented with information about the illness. Such a discussion helped to preclude adverse reactions to popular articles on the subject and also helped to enlist the patient's active participation in

a medical regimen. Indiscriminate information about the poor prognosis for adolescents unnecessarily intensified fears and created additional adjustment problems. Much information about the patient's adjustment to the disease could be obtained from his attitude toward taking medication. This was illustrated with brief notes from the anamnestic data. Many of the adjustment problems could be understood in terms of the reactions to fear and dependency. A third consideration was the interpretation of the process, based on emotional problems that were concentrated upon at the time of the onset of the disease. In some instances specific problems may occur that are based on the involvement of an organ that has special meaning to the patient. The symptoms of myasthenia gravis were intensified by emotional upsets. These more specifically seemed to involve anger and envy. Their effect was possibly a direct one on the skeletal musculature. 1 reference.—*Author's abstract.*

ANATOMY AND PHYSIOLOGY OF THE NERVOUS SYSTEM

109. *The Babinski Response: A Review and New Observations.* P. W. NATHAN AND MARION C. SMITH, London, England. J. Neurol., Neurosurg. & Psychiat. *18*:250–259, Nov., 1955.

An account is given of Babinski's contributions to the study of the normal plantar response and the response named after him. The literature correlating the normal plantar response and the Babinski response with the state of the corticospinal tract (as shown histologically) is reviewed and summarized. A correlation of the plantar response with proved lesions of the spinal cord due to the operation of anterolateral cordotomy is presented. This material shows that any lesion of the lateral and ventral columns of the cord may, or may not, cause the Babinski response, that conclusions cannot be drawn with regard to the tract involved when the Babinski response is found, that the Babinski response is often found with histologically normal corticospinal tracts, that a lesion of one side of the cord may be associated with a Babinski response on the opposite side of the body, that lesions of the anterior half of the cord may accompany the Babinski response, that apparently identical lesions on the two sides of a spinal cord may be associated with a normal plantar response on one side and Babinski response on the other, and that small bilateral lesions are more likely to cause a Babinski response than large unilateral lesions. 39 references. 7 figures.—*Author's abstract.*

110. *Is Pain Due to Pressure on Nerves?* MICHAEL KELLY, Melbourne, Australia. Neurology *6*:32–36, Jan., 1956.

The pressure theory of pain is widely accepted because it has not been critically examined. In different cases different mechanisms are called by the name "pressure." Pain of unknown origin is frequently attributed to pressure on nerve trunks or roots. However, tumors that invade these tissues are frequently painless; therefore, pressure cannot be the primary stimulus. Pressure is often a secondary factor in tissues already hyperalgesic.

If pressure on roots is not a common pain mechanism, it is possible that a protruded inter-

vertebral disc is not a common cause of sciatic pain. The evidence of many authors suggests that protrusion of a lumbar disc is very common and that it is not pathologic. Discs frequently press on nerve roots without causing symptoms; prolapsed fragments are frequently invaded by granulation tissue and shrink away.—*Author's abstract.*

CEREBROSPINAL FLUID

111. *Effect of Urea on Cerebrospinal Fluid Pressure in Human Subjects: Preliminary Report.* MANUCHER JAVID AND PAUL SETTLAGE, Madison, Wis. J.A.M.A. *160*:943–949, March 17, 1956.

Though urea, administered by the oral route in doses of 20 Gm. two to five times daily, is used as a diuretic in human subjects, there have been no previous studies of its effect on intracranial pressure in man.

In the present study 30 per cent urea in 5 per cent dextrose was administered intravenously to 21 patients. The solutions were prepared by dissolving sterile crystals in the required amount of sterile 5 per cent dextrose in water. It is emphasized that urea may not be sterilized by boiling or autoclaving, since heat produces decomposition, and it is suggested that the toxic effects of intravenous administration which have been observed in animal studies may have been due to use of heated or stale solutions. Small doses, 100 Gm./Kg. of body weight, were used in the early phases of the study, and, as it became apparent that no toxicity was produced, the dosages were increased up to a maximum of 1000 mg./Kg. One patient received urea intravenously and orally and was also given 50 per cent sucrose for comparison.

In most cases cerebrospinal fluid pressure was measured for periods of four to six hours. The study included a preliminary survey of the course of changes in blood and spinal fluid urea levels following injection.

It was found that urea, in all dosages, always produced a prompt fall in cerebrospinal fluid pressure, with the larger doses producing large and sustained decreases. The absolute magnitude of the pressure change was found to be strongly influenced by the pressure level that was present prior to injection. A high initial pressure was followed by a more profound drop than that which occurred in the presence of a normal preinjection level. In 2 cases the pressure dynamics following urea injection were interpreted as suggesting that the reduction in brain bulk must have been of such a degree as to result in opening of a block in the cerebrospinal fluid pathway. In the 1 case in which comparisons were made, gastric administration of 600 mg. of urea/Kg. of body weight was observed to be about as effective as intravenous administration of this same dose, and this dose of urea proved to be much more effective than 100 ml. of 50 per cent sucrose.

The blood urea levels found following administration of urea were unremarkable. The highest level observed was 90 mg./100 ml., and the available evidence indicated that the blood clears to preinjection levels in about 12 hours. Also, there was some indication that cerebrospinal fluid urea does not return to preinjection levels until some time after the blood has cleared.

Though it was noted that there was temporary symptomatic improvement in some of the patients, the study did not include any attempt to assess the therapeutic possibilities of urea. 18 references. 4 figures. 2 tables.—*Author's abstract.*

CONVULSIVE DISORDERS

112. *Behavior of Epileptic and Nonepileptic Patients with "Temporal Spikes."* FRANK ERVIN, ARTHUR W. EPSTEIN, AND H. E. KING, New Orleans, La. A. M. A. Arch. Neurol. & Psychiat. *74*:488–497, Nov., 1955.

Forty-two patients with electroencephalographic findings of a "temporal spike" were subjected to psychiatric and neurologic examination. Twenty of these patients who had no previous history of seeking help from psychiatric or other counseling facilities were, in addition, subjected to psychologic testing. It was hoped that investigation of such a group of patients would offer an approach to the correlation of disturbed behavior with known cerebral dysfunction.

Of the patients investigated, 34 were given a diagnosis of schizophrenia, 10 of these showing primary symptomatology as outlined by Bleuler and 24 showing secondary symptoms of structured delusions or hallucinations.

Thirty-one patients had clinical epilepsy, 22 of whom had "idiopathic" psychomotor seizures occurring either alone or in combination with grand mal seizures. Of the 9 patients who had no clinical seizures, 7 were schizophrenic, and, of these, all had had acute overt psychotic reactions in contrast to only five such acute episodes in the other 33 patients.

Twenty-nine of the 42 patients showed "episodic symptoms," such as sudden affective changes, alterations in consciousness (for example, *déjà vu* or fugue states), and hallucinations. Nonepisodic symptoms were chiefly paranoid, hypochondriac, or referential, and, in addition, there were many depressive and hysterical symptoms. Eight individuals showed persistent visceral symptoms, and 11 were specifically noted to be hyperactive. Eight of the 14 patients with complex psychomotor seizures were considered to show "organic" changes, such as paraphasia and dyscalculia on mental testing.

Characterologically the group was distinguished by loosely organized and immature patterns of adaptation. All observers emphasized that this group of patients was more severely disturbed than a simple statistical breakdown can convey.

Of the 7 patients who had acute psychotic episodes, 5 were primarily catatonic, while none of the rest of the group examined had shown such reactions. The question is raised as to whether or not there is indeed some reciprocal relationship between the presence of seizures and the presence of this particular kind of psychotic reaction.

On testing with Rorschach, the psychomotor performance test, and behavior ratings, the 20 patients who had no history of overt behavior disorder showed a marked deviation from normal, most pronounced in the group with complex psychomotor seizures. These abnormalities were confirmed on clinical examination and noted to be just as intense and frequent as the abnormalities seen in the group of patients who had had professional help for behavioral disturbance.

It is noted that there is a continuum of episodic behavioral disorder ranging from transient visceral symptomatology and changes in consciousness to transitory psychotic phenomena such as hallucinations to true epileptic seizures and/or overt psychotic reactions. The presence of such a continuum suggests that there may be a parallel physiologic change in such states. The importance of the relationship between seizures, dreams, and psychosis as pointed out by John Hughlings Jackson is once again emphasized.

It is suggested that the EEG abnormality in these patients may be related to subcortical electrophysiologic disturbances as reported in psychosis by Bickford, Brazier, Delgado, Heath, and others.

It is emphasized that such behavioral studies in persons with altered central nervous system function are important for the further understanding of normal behavior. 14 references. 5 tables.—*Author's abstract.*

113. *Mongolism and Convulsive Seizures.* RICHARD D. WALTER, Los Angeles, Calif., CHARLES L. YEAGER, AND HARRY K. RUBIN, San Francisco, Calif. A.M.A. Arch. Neurol. & Psychiat. *74*:559–563, Nov., 1955.

It has long been recognized that epileptic seizures are rare as a symptom in Mongolism. This is somewhat surprising in view of the concept that the neuropathologic changes in this disease are essentially the same as those found in other categories of undifferentiated mental deficiency. To investigate further the rarity of seizures in Mongolism, a review was made of 200 clinical records in which the diagnosis was fairly well established by an experienced staff. The incidence was found to be 2.0 per cent for convulsive seizures.

In addition, 30 Mongols and 30 patients with undifferentiated mental deficiency without clinical seizures were studied electroencephalographically with activation techniques. The photomyoclonic threshold for the group of Mongols averaged 6.9 mg./Kg., while the undifferentiated mental defectives averaged 4.7 mg./Kg. The routine recordings on 83 patients with Mongolism and 84 patients with undifferentiated mental deficiency were compared. Seventy-seven per cent of the records were normal in the group with Mongolism, in contrast to 46 per cent normality in the control series. It was concluded that not only is there a relatively low incidence of seizures in Mongolism as a group in mental deficiency, but also that Mongols have a higher photomyoclonic threshold. The neuropathologic changes found in both Mongolism and undifferentiated mental deficiency do not seem to explain this disparity in seizure activity. 8 references. 1 figure. 3 tables.—*Author's abstract.*

114. *Treatment of Petit Mal Epilepsy (Zur Praxis der petit mal Epilepsiebehandlung).* RUDOLF DREYER. Nervenarzt *26*:225–228, June 20, 1955.

Trimethadione, employed in the treatment of petit mal epilepsy, gave best results in children up to 12 years of age; in adolescents the results were not so satisfactory, and in adults, good results were rarely observed. In cases of petit mal epilepsy in which there were frequent attacks, 2 capsules of trimethadione were given the first day, and the dosage was increased by 2 capsules every day or every other day until the attacks ceased; in some cases 4 to 6 capsules a day were sufficient to control the attacks, in other cases 8 to 10 cap-

sules were required; in very young children the dosage was rarely increased above 2 or 3 capsules daily. After all attacks ceased, the dosage could be gradually reduced until the dosage necessary to maintain freedom from attacks was determined. In some cases small doses of caffeine combined with trimethadione, and in others a combination of acetazolamide and trimethadione, gave more favorable results than trimethadione alone. Blood counts should be made during prolonged trimethadione therapy, at first as often as every eight days, later at four to eight weeks' intervals. Skin reactions may occur that make it necessary to discontinue use of the drug. Other reactions, such as photophobia, headache, and gastrointestinal symptoms, can usually be controlled by reducing the dosage or by combining it with caffeine. In all cases, psychotherapeutic measures are necessary, including interviews not only with the patient but also with the parents. As trimethadione frequently controls entirely petit mal attacks or definitely diminishes the frequency of such attacks, it is to be considered a valuable drug for use in this form of epilepsy. 4 references.

DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

115. *Studies in Myasthenia Gravis—A Rapid Diagnostic Test.* KERMIT E. OSSERMAN AND PAUL TENG, New York, N. Y. J.A.M.A. *160*:153–155, Jan. 21, 1956.

Edrophonium chloride is a cholinergic drug characterized by prompt, brief action on patients with myasthenia gravis. The response consists of a temporary increase in muscle strength and general subjective improvement. If the diagnosis has been correct, there is no ensuing fasciculation in the muscles and side effects are minimal. If the subject is psychoneurotic with abnormal fatigability, the effects of the drug can be duplicated by giving a placebo. If the subject is normal, there is usually fasciculation without increase in strength. Excessive doses of the drug elicited false-negative reactions in a small group of hyperreactive subjects. The recommended dosage, based on a study of 300 patients, consists of 2 mg. injected intravenously, to be followed 30 seconds later by an additional 8 mg. if the first portion does not elicit a reaction. 6 references. 1 figure.—*Author's abstract.*

116. *A New Scale for Evaluating Disability in Multiple Sclerosis.* JOHN F. KURTZKE, New York, N. Y., Neurology *5*:580–583, Aug., 1955.

Based upon the evaluation of 315 patients with multiple sclerosis, a rating scale was devised with categories from 0 through 10, each category designed to measure maximal function as limited by neurologic deficit. Status 0 comprised those with normal neurologic examination; status 1, those who were asymptomatic but with abnormal signs; status 2, those with minimal dysfunction, usually monosymptomatic. In status 3 were those with a combination of minor symptoms or one more severe complaints; status 4 included those with greater dysfunction but with ability to be up and about at least 12 hours a day. In status 5 were those too handicapped to function well throughout the day but not yet needing aid for ambulation; status 6 comprised those who needed aid to walk; status 7, those

restricted to a wheelchair but self-sufficient therein. In status 8 were those unable to get out of bed without the aid of an attendant, but who still had some useful limb function, usually of the arms. In status 9 were the helpless, bedridden patients, and in status 10, those whose death was primarily caused by multiple sclerosis.

The scale seemed to depict adequately the varying degrees of disability in different patients, to be quite simple, and to reflect appropriately changes in the individual patient over the course of time. 4 references. 2 figures.—*Author's abstract.*

117. *Treatment of Myasthenia Gravis with Mestinon Bromide.* JOSEPH E. TETHER, Indianapolis, Ind. J.A.M.A. *160*:156–158, Jan. 21, 1956.

Mestinon bromide (a dimethyl carbamate of 3-hydroxy-1-methyl pyridinium bromide) was used in treatment of 165 patients with myasthenia gravis. Duration of therapy ranged from 3 to 17 months. Severity of symptoms ranged from mild to extreme. Dosage varied from 60 mg. daily in the mildest to 6000 mg. in the most severe case.

All patients had previously been treated with neostigmine. Most of them preferred Mestinon because of its smoother, steadier, apparently more prolonged effect and its less severe side effects. Mestinon in excess usually produces, in addition to sweating, salivation, and mild abdominal symptoms, rather definite muscle fasciculations, a peculiar blurring or "jumping" of vision with mild vertigo, and, occasionally, a "thick tongue" sensation with dysarthria and dysphagia. If these symptoms are ignored and even more medication is taken, increased weakness may occur which may involve the muscles of respiration and result in a cholinergic crisis, difficult to distinguish from true myasthenic crisis. In most cases, symptoms of Mestinon overdosage are clear enough to serve as warning signals, especially if patients are trained to recognize them.

No organic toxic effects due to Mestinon were noted regardless of dosage or length of administration. 3 references. 1 table.—*Author's abstract.*

118. *Presenile Dementia of the Jakob Type.* S. BORNSTEIN AND GEORGE A. JERVIS, Montrose, N.Y. Arch. Neurol. & Psychiat. *74*:598–610, Dec., 1955.

Creutzfeldt and Jakob were the first to describe those presenile dementias with neurologic symptoms that Wilson later named cortico-strio-spinal degeneration. Two cases were observed that illustrate extreme varieties of this disease, one in which neurologic symptoms, and another in which mental deterioration, dominate the clinical picture. The first patient presented a picture of amyotrophic lateral sclerosis with psychosis. The other patient appeared to suffer from Alzheimer's disease.

The brain, in both cases, showed mild cortical atrophy grossly. Microscopically, degenerative changes and loss of nerve cells, astroglial proliferation, and, in the deeper layers, satellitosis and neuronophagia were seen in the cortex. These changes were spotty in the first specimen, while they showed a predilection for the orbital region in the second. Much sudanophilic material was found in the large nerve cells. Extensive cellular degeneration in the basal ganglia of both brains involved mostly the large cells, also in the anterior horns of the first and in the thalamus and subthalamus of the second case. Senile plaques were

present in the basal ganglia of the first patient only, and not in the cortex; there were no Alzheimer bodies in either brain.

Twenty-six cases of cortico-strio-spinal degeneration from the literature on which anatomic studies have been reported were tabulated. It can be seen that they are clinically characterized by a progressive intellectual deterioration that starts in the fifth and sixth decade and followed by death within two years. Speech disturbances are almost always present. Other neurologic symptoms, namely, spasticity, tremors, athetosis, ataxia, or amyotrophy, vary greatly or may be absent. Grossly, slight atrophy of the cerebral cortex may be visible. Microscopically, a diffuse, focally accentuated degeneration of nerve cells is present that consists of swelling, fatty or pigmentary degeneration, shrinkage, or complete destruction, usually with reactive neuroglial proliferation. These changes are always to be found in the cortex, and they may involve, with much variation in intensity, the basal ganglia, the thalamus and motor nuclei, or cerebral and spinal nerves. Demyelinization, if present, is of minor importance.

Kraepelin's and Heidenhain's diseases belong in this group. They vary from other cases merely by their rapid course or by the localization of the most severe degeneration. For the classification of cases within this group the terms "spinal-strio-cortical" and "strio-cortico-spinal" degeneration are suggested. 31 references. 8 figures. 1 table.—*Author's abstract.*

ELECTROENCEPHALOGRAPHY

119. *Electroencephalographic and Neuropsychiatric Observations in Patients with Senile Cataract.* HANS STRAUSS, LOUIS LINN, AND MORTIMER OSTOW, New York, N. Y. Monatschr. f. Psychiat. u. Neurol. *130*:321–327, Nov., 1955.

Electroencephalographic studies were made on 22 patients after operation for senile cataract; prior to operation careful clinical examination had shown no neurologic or psychiatric disturbance, but the amobarbital sodium test on 19 of these patients indicated organic brain disease in 14. The electroencephalographic findings were normal in 10 and abnormal in 12 patients. In 8 of the 12 abnormal electroencephalograms there were bursts of slow activity, most marked at the ear lobe and anterior temporal electrodes; the other 4 showed irregular slow activity. In a control group of 13 patients 70 years or older without senile cataract, and without clinical signs of organic brain disease, the electroencephalographic findings were normal in 10 and abnormal in 3 patients; only 1 of these 3 patients showed bursts of slow activity, and these were not in the same area as in the patients with cataracts. In a larger group of patients the electroencephalograms showed bursts of slow activity to be a rare abnormality, noted in 3.5 per cent only. Clinically severe psychic reactions after the cataract operation were observed in 10 of 11 patients with abnormal electroencephalographic findings and in only 4 of 9 patients with normal findings. The high percentage of abnormal findings in patients with senile cataract indicates that there is, in these cases, some particular type of degenerative disorder affecting both the brain and the crystalline lens; the exact nature of this disorder is unknown, but the authors suggest that

it be called "lentocerebral degeneration." 6 references. 2 figures. 2 tables.—*Author's abstract.*

120. *Changes in a Circumscribed Area in the Electroencephalogram after Slight Head Injury in Children (Ausgeprägte Herdveränderungen in Hirnstrombild nach leichten Schädeltraumen bei Kindern).* A. WALKENHORST. Nervenarzt 26:250–251, June 20, 1955.

In 2 girls, 2 and 7 years old, with a slight head injury, the electroencephalogram showed delta waves of unusual amplitude and height, indicating an injury in the medullar layer rather than in the cortex in the region of the injury. Both children showed a hemiparesis after the injury. Arteriography and encephalography did not indicate a localized injury. It is possible, however, that some minor anomaly of the cerebral blood vessels resulted in some intracranial bleeding without definite localization; this seemed very probable, especially in the older child. 2 figures.

121. *Electroencephalographic Changes in Man Correlated with Blood Alcohol Concentration and Some Other Conditions Following Standardized Ingestion of Alcohol.* GUNNAR HOLMBERG AND STEN MARTENS, Bromma, Sweden. Quart. J. Stud. on Alcohol *16*:411–424, Sept., 1955.

In the study reported, a standardized dose of ethyl alcohol (1.25 Gm. alcohol/Kg. of body weight) was given to 10 male hospital attendants and 10 male patients hospitalized for alcoholism. The ages of the hospital attendants varied from 20 to 38 years; the patients were older, their ages varying from 32 to 50 years. When the study was begun, the patients had been in the hospital for several weeks and had recovered from the acute sequels of alcoholic intoxication. In all the 20 subjects the electroencephalograms were within the limits of normal variation when the study was begun. Determinations of blood alcohol concentrations and degree of ataxia, electroencephalograms, and electrocardiograms were made at regular intervals for four and a half hours in all subjects. The concentration of alcohol in the blood was much the same in both groups of subjects, ranging from 108 to 196 mg./ml. It tended to be only slightly higher in the patients than in the hospital attendants. The electroencephalographic frequencies showed slower ranges (averaging 1.4 to 1.5 cycles/second) but increasing amplitudes (increase of 50 to 100 per cent) after the ingestion of alcohol. While the difference between the two groups of subjects was not statistically significant, the slowing of the frequencies was a little less marked in the patients. The maximum electroencephalographic changes in the patients occurred when the blood alcohol concentration was at its maximum, but in the hospital attendants these changes persisted for 45 minutes after the alcohol concentration in the blood was at a maximum. The electrocardiograms showed a short excitation, followed by retardation that was most marked in the hospital attendant group. The alcohol administered to this group frequently caused nausea and drowsiness, and the electrocardiograms showed a new abrupt excitation with nausea, followed by another decrease with the drowsiness. Nausea and drowsiness rarely occurred in the patients after the administration of alcohol, and the electrocardiographic changes were accordingly less marked and less complex. The degree of ataxia caused by

the test dose of alcohol was less marked in the patients than in the hospital attendants. The differences observed in the two groups of subjects is explained by greater habituation of patients to alcohol rather than to the fact that they were an older age group. 15 references. 6 figures.

122. *The Electroencephalogram in Infantile Cerebral Palsy.* MEYER A. PERLSTEIN, ERNA L. GIBBS, AND FREDERIC A. GIBBS, Chicago, Ill. Am. J. Phys. Med. *34*:477–496, Aug., 1955.

An electroencephalographic study was made on 1217 consecutive patients with infantile cerebral palsy. In this study, several observations and conclusions have emerged.

Of the total cerebral palsy population, the incidence of spastics over athetoids was three to one. Whereas deafness was found in only 2 per cent of the spastic population, it was present in 16 per cent of the athetoids. When the athetoids were divided into two groups, those due to the Rh factor and those due to other causes, it was found that deafness occurred in 32 per cent of the former and only 8 per cent of the latter.

It is not surprising that seizures are much more common in cerebral palsy than in the normal population. In spastics, exclusive of paraplegics, they occurred in more than 60 per cent of the patients. Seizures occurred in only about 20 per cent of the athetoids and about 30 per cent of the spastic paraplegics. Whereas the most common type of seizure in epileptic children is the petit mal spell, the most common in cerebral palsy is grand mal. The electroencephalograms were abnormal in more than 90 per cent of the cerebral palsy patients with seizures. What is more surprising, however, is that abnormal electroencephalograms occur twice as frequently in spasticity as in athetosis. In fact, the presence of a normal electroencephalogram in a seizure-free patient with cerebral palsy weights the probability two to one that the patient is an athetoid rather than a spastic. Spike seizure discharges are the most common electroencephalographic abnormalities seen in the cerebral palsy patient, occurring more commonly in cerebral palsy than in epilepsy. There is a high degree of correlation between the laterality of the clinical findings and the electroencephalographic findings. Particularly in hemiplegia, one should pay attention to the presence of asymmetries in the electroencephalogram. The significance of unilateral suppression of voltage or unilateral decreases of the 14 per second sleep spindles and of biparietal humps or in alternation of normal sleep patterns from side to side, as electroencephalographic abnormalities, has been demonstrated. In contrast to the findings in unselected epileptics, the spike seizure discharges in the electroencephalograms of cerebral palsy patients have a focal or a symmetric distribution. Occipital spikes are the most common focal lesion and their presence is highly correlated with the presence of clinical strabismus. One of the significant observations has been the tendency for the electroencephalographic findings to change with age. The greatest number of abnormal electroencephalograms are seen in the age group of 4 to 6 years. Whereas the most common site of pathology in infancy is the occipital area, migration occurs with advancing age to the mid-temporal, then to the parietal and thalamic areas at puberty, and finally to the frontal or anterior temporal areas in adulthood. In many instances, complete normalization of the electroencephalogram tends to occur before the sixteenth year.

The character of the electroencephalographic abnormality may throw light on the nature of some of the episodic behavioral disturbances that occur in children with cerebral palsy. Occasionally, these disturbances may represent subclinical equivalents of epileptic seizures. 9 references. 17 figures. 10 tables.—*Author's abstract.*

For Reference

123. *Brain Waves and Problems of Psychology.* ROBERT J. ELLISON, Omaha, Neb. Psychol. Bull. *53*:1–34, Jan., 1956.

HEAD INJURIES

For Reference

124. *Motivation of the Brain Damaged Patient.* G. IRENE GREER. Am. J. Occup. Therapy. *9*:156-157, July-Aug., 1955.

INFECTIOUS AND TOXIC DISEASES OF THE NERVOUS SYSTEM

For Reference

125. *Cysticercosis of the Brain and Spinal Cord (Die Zystizerkose des Gehirns und Rückenmarkes).* ALBERT HUHN, University of Cologne. Fortschr. d. Neurol., Psychiat. *24*: 7–27, Jan., 1956.

INTRACRANIAL TUMORS

126. *Intracranial Neoplasms Masked as Depressions and Diagnosed with the Aid of Electroencephalography.* HANS STRAUSS, New York, N. Y. J. Nerv. & Ment. Dis. *122*:185–189, Aug., 1955.

Clinical and electroencephalographic observations on 4 patients are reported. These patients sought medical attention because of depressive states and were treated for their depressions with psychotherapy, drugs, and electroconvulsive therapy. Two patients seemed entirely normal on careful neurologic examination, but minor neurologic signs were found after the electroencephalogram had directed attention in a definite direction. In 2 other patients, abnormal electroencephalographic findings aroused suspicion of organic cerebral disease, and neurologic examination led to the diagnosis of intracerebral tumor. The role of various factors (personality, environment, and cerebral lesion) in the etiology of the depressive state is discussed. 12 references.—*Author's abstract.*

NEUROPATHOLOGY

127. *Differential Diagnosis of Pick's Disease and Alzheimer's Disease on the Basis of 12 Cases Studied Clinically and Anatomically (Le diagnostic differentiel des maladies de Pick et d'Alzheimer à propos de 12 observations anatomo-cliniques).* J. DELAY, S. BRION, AND J. GARCIA BADARACCO, Paris, France. Encéphale *44*:454–499, 1955.

In the study of 7 cases of Alzheimer's disease and 5 cases of Pick's disease, all verified by histologic examination, definite clinical differences between the two diseases were found. In Alzheimer's disease, loss of memory and disturbances of orientation in space and time are characteristic symptoms, followed by the development of a syndrome of aphasia, apraxia, and agnosia. In Pick's disease there is gradual mental deterioration, but not the disturbances of memory or orientation observed in Alzheimer's disease. In Alzheimer's disease, histologic studies showed cortical atrophy, which was present in all regions but not of marked degree in most areas; the lesions were especially marked in the region of Ammon's horn. In Pick's disease, the cortical atrophy was localized in the frontal and temporal regions; there was marked gliosis; and the lesions in the region of Ammon's horn were different from those seen in other parts of the cortex, showing a swelling of the cells even when atrophic changes were marked in other regions. 52 references. 25 figures. 1 table.—*Author's abstract.*

TREATMENT

128. *Procaine Oil Blocking of the Globus Pallidus.* H. NARABAYASHI, T. OKUMA, AND S. SHIKIBA, Tokyo, Japan. A.M.A. Arch. Neurol. & Psychiat. *75*:36–48, Jan., 1956.

Experiences are reported of the operation on the globus pallidus in 26 cases of Parkinson's syndrome, 5 of which were of the paralysis agitans type and 2 of the postencephalitic parkinsonism type; the nature of the other cases remained obscure in nature. The globus pallidus is punctured by using the author's own stereotaxic instrument, which is applied with the patient in the supine position. Through the hole of the needle, which is 1 mm. in diameter, 0.5 to 1.0 ml. of procaine hydrochloride suspension in oil and wax is injected to the nucleus, which is considered to be safer than electrolysis and to have more prolonged local narcotic effect than its aqueous solution.

Two main symptoms of this disease, namely, rigidity and tremor, were dramatically improved and, in some cases, completely abolished immediately after injection without producing any undesirable side effects, such as palsy. With these improvements, the patient's voluntary movements showed marked improvement, especially in writing, walking, posture, and speech. Three years of postoperative observation make it clear that improvement of rigidity is sustained but that the postoperative reduced tremor begins to reappear within several weeks after the surgery. Vegetative symptoms were also improved in most cases.

Only 1 patient died; this was caused by intracerebral bleeding during insertion of the

needle. The only notable side effect was supranuclear palsy in a beginning few cases. From these facts, the authors consider the globus pallidus to play an important accelerating role in producing the hypertonic state of the muscles. 63 references. 8 figures. 1 table. — *Author's abstract.*

For Reference

129. *Results in the Treatment of Huntington's Chorea with Procaine Amide Hydrochloride.* J. A. LAZARTE, C. W. BAARS, AND J. S. PEARSON. Am. J. M. Sc. *229*:676–677, June, 1955.

BOOK REVIEWS

Medical Research: A Midcentury Survey. Edited by ESTHER EVERETT LAPE, Member-in-Charge, American Foundation. Vol. 1: *American Medical Research in Principle and Practice.* 765 pp. Vol. 2: *Unsolved Clinical Problems in Biological Perspective.* 740 pp. Boston, Mass., Little Brown & Co., 1955. $15.00 the set.

These two substantial volumes present the results of 15 years of collecting and digesting data on basic medical research in the United States and on some of the unsolved clinical problems. Since it is obviously impossible to summarize so comprehensive a summary, a few general remarks only are offered.

The emphasis throughout is on the biologic, chemical, physical, and mathematical aspects of medical research—the aspects that lend themselves readily to measurement and controlled observation. This is quite proper; indeed, only one psychiatric topic, namely, the biology of schizophrenia, is discussed in detail, and treatment of the psychologic approach there occupies nearly one third of the chapter.

The scope of the chapters is little short of astounding. The material from countless sources is well arranged and presented in readable form with a minimum of editorializing. The material, too, is decidedly up to date, whether it has to do with the effects of the security program on research or the use of the tranquilizing drugs. Such varied aspects of research as cybernetics, the financing of projects, scientific literature, and the functioning of the Food and Drug Administration are discussed with fulness and clarity.

In volume 2, after an initial chapter on Current Metabolic Concepts, follow chapters on Cancer, Infertility, Arteriosclerosis, Hypertension, The Rheumatic Syndromes, Tuberculosis, Viruses and Virus Diseases, Alcoholism, and Schizophrenia. It is not implied that these are *all* the unsolved problems. Some would place the general biologic problem of aging, for example, well to the fore, even though cancer and arteriosclerosis are among the incidents of that process.

The chapter on alcoholism, consistently enough, is devoted largely to a consideration of the metabolic approaches. The editor notes that alcoholism is an outstanding psychologic and social problem and notes also the need for multifaceted research, including social and psychologic research. There is a brief discussion of psychotherapy and Alcoholics Anonymous.

In the chapter on schizophrenia it is pointed out that of all the mental illnesses schizo-

phrenia is the "number one riddle," and, for this reason, this particular group of disorders is taken as the exemplar of mental illness in general. The discussion of the biologic aspects is comprehensive and should be read by all psychiatrists. Rarely does one find any discussion of psychiatry that is so thought provoking and truly orienting, at the same time being so brief and clear. Among the needs suggested are adequate controls (patients and normal persons) and consistent recognition of variables in the patient, the tester, and the environment. Some pungent comments are made on the insularity of the terminology and on the use of terms that "define too little and connote too much. . . . In its present isolated psychodynamic trend it [psychiatry] is regarded by some medical educators as not a scientific or teachable discipline and as thus having no proper place in the medical school curriculum" (p. 669). There is a brief discussion of the various therapies (note that group psychotherapy was used by Pratt, Wender, Moreno, and others long before World War II), and the significance of social and cultural studies is not overlooked.

The sources of information are listed alphabetically at the end of each volume, and references are given for practically all of the statements made.

All who are interested in reviewing the accomplishments of medical research or in gaining insight into the prospects for the future should read these volumes attentively and at the same time thank the American Foundation, the editors, and the distinguished Committee of Consultants for an extraordinary job outstandingly done.—*Winfred Overholser, M.D.*

The Psychology of Personality. BERNARD NOTCUTT. New York, N. Y., Philosophical Library, Inc., 1953. 235 pp. $4.75.

This is a description and evaluation of psychologists' activities in regard to personality and its components and techniques of assessment. The trends of the present century are analyzed. Only the last chapter deals with earlier, prescientific views of the nature and determinants of personality. Nevertheless, it might be called a history of the psychology of personality.

Because of its extensive bibliography, good tables, and useful way of arranging the material in meaningful order, the book could serve as a guide for teachers giving a course in psychology of personality. The author has skillfully integrated a wide knowledge of literature, both American and European, and has brought out the essential "current psychological concepts and methods that have the best promise for the future." However, it is regrettable that the breadth of knowledge does not always coincide with depth of understanding of the material under discussion.

The book also provides an excellent opportunity for the practicing psychologist, whatever his field of specialization, to study the various approaches to personality study. The reader may be able to identify the basic trends of his thoughts and activities and find his place in the general development.

Various constructive suggestions are made in the last chapters in regard to methods that may further our understanding of personality. In a sensible middle-of-the-road fashion a synthesis of subjective and objective psychology is suggested. The author's opinion is: "So far the subjective psychologists have had the most of the interesting ideas, but have been distressingly unable to prove them. The objective psychologists have made delicate

instruments of analysis, but have applied them to trivial problems. . . . The prosperous future of psychology depends on a proper blending of insight and validation" (p. 217-218).

Unfortunately, constructive ideas come forth only in a small fraction of the book and may escape many readers since the first four chapters express such a caustic, cynical attitude toward serious efforts in our field that one is tempted to lay the book aside.—*Mirjam Mueller-Zbylut, Ph.D.*

Counseling Psychology. MILTON E. HAHN AND MALCOLM S. MACLEAN. Ed. 2, New York, N. Y., McGraw-Hill Book Company, Inc., 1955. 302 + xi pp. $4.75.

The authors have attempted to present a comprehensive outline of the history, training, ethics, and functions of counseling psychology and have also attempted to define the relationship that exists between it and related disciplines. However, recognizing the impracticability of discussing extensively each aspect of the counseling profession, chapter topics are supplemented with an extensive bibliography.

Of special interest is the penetrating discussion of the factors determining predictability in educational and vocational counseling. This includes a consideration of the field-level concept and the necessity to use specific aptitude tests rather than general intelligence measures.

Unfortunately, while the authors state: "The purpose of this book is to focus upon counseling with individuals who are faced with vocational-educational-personal problems" (p. 42), they give emphasis only to those procedures that are usually associated with the vocational-educational aspects of counseling. Justification for this attitude appears to reside in their belief that counselors working in educational institutions must of necessity restrict the nature of their work. This, however, minimizes the influence that emotional make-up can have upon educational and vocational maladjustment.

The authors also state: "His right [the counselor's] to tell a counselee what he can, must, or should do is legitimately questioned [by the counselee] sometimes with great heat" (p. 203). The authors, no doubt, do not intend to convey this impression, but certainly this does not suggest that the counselor is more concerned with the reactions within the counselee than he is with transmitting his supposedly valid test results. This impression is further conveyed in the subchapter where counseling techniques are discussed (Forcing Method). It is unfortunate, but the semantics certainly do not convey the idea of two people working together and certainly can confuse the neophyte as to the role and function of counseling.

Finally, confusion and misinterpretation may arise from the implication that counseling psychologists are adequately trained to employ projective techniques and that the primary function of the clinical psychologist is psychotherapy. Both, of course, are false. Most counseling psychologists are not prepared adequately to utilize projective techniques, and a major part of the clinical psychologist's job is that of a psychodiagnostician.

There are within certain educational institutions attempts to minimize the emotional implications of educational and vocational maladjustment. To those institutions and to the individuals who adhere to this philosophy this book is highly recommended as a basic text. To others in the field of counseling it is felt that this text can offer much thought-provoking material.—*George Lassen, Ph.D.*

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

&

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

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JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

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JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY

OCTOBER–DECEMBER 1956

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Psychobiology—1956: Physiodynamic Psychiatry in the Light of Pharmacodynamic Advances

In Memoriam

Symposium on Artificially Induced Psychoses

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

Incorporating the International Record of Psychiatry and Neurology

PSYCHIATRY ABSTRACTS

Statement of Purposes

The JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY and QUARTERLY REVIEW OF PSYCHIATRY and NEUROLOGY are dedicated to the search for the fundamental factors in the etiology and pathogenesis of psychiatric disorders; to the training of an alert, progressive, and qualified psychiatric personnel; and to the stimulation and support of all phases of psychiatric service and research—biologic, chemical, psychologic, physiologic, and social.

In the pursuit of these aims, the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY and QUARTERLY REVIEW OF PSYCHIATRY and NEUROLOGY will venture wherever the quest may lead. Its sole criterion will be the promise of an increment in the understanding of the mind's ills. It will seek, above all, to bridge national boundaries, language barriers, and the artificial demarcations of schools and trends.

The JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY and QUARTERLY REVIEW OF PSYCHIATRY and NEUROLOGY hold that there is no justification for the present discrepancy between the rich scientific technology available to psychiatry and the poverty of techniques in current use in diagnosis, treatment, and research; no need for the gap between the promise of research and the paralysis of inquiry; no excuse for the lag of years between discovery and publication, demonstration and application in practice; no sound reason for the tragic chasm between the desire of the public for psychiatric education and guidance and the failure of the profession to provide the inspiration and leadership that would fully mobilize all latent potentialities. In brief, the journal is dedicated to the fulfillment of psychiatry as a science and a humanity devoted to the interests of all mankind.

The JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY and QUARTERLY REVIEW OF PSYCHIATRY and NEUROLOGY look on psychiatry as an integral whole that is, in turn, an organic part of the world of science. It seeks to be not a mere sheaf of passive paper, but a dynamic organism by means of which its Editorial Board will endeavor to utilize every opportunity and facility in the field of human knowledge to fulfill the tasks to which it is dedicated.

JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY
&
QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

PSYCHOBIOLOGY—1956

PHYSIODYNAMIC PSYCHIATRY IN THE LIGHT OF PHARMACODYNAMIC ADVANCES

On Problems and Perspectives in Biologic Psychiatry*

Mortimer D. Sackler, M.D., and Raymond R. Sackler, M.D.

THE VAN OPHUIJSEN CENTER
NEW YORK, N. Y.

The year 1956 is notable not only as the centennial year for two giants in psychiatry, Kraepelin and Freud, but also as the year in which a resurgence of biologic emphasis has created new vistas for the further development of scientific psychiatry. The century of progress in psychiatry that has just been completed is marked by two major developments that have paved the way for further advance. Kraepelin fused his medical training with his interest in experimental psychology, nosology, and the natural history of mental disorders. He utilized his clinical skills to establish an inventory of psychologic disturbances and so made possible the classification of psychologic disorders. Freud, with his attention directed toward psychologic energetics and symptoms, gave us profound insight into the dynamics of symptom formation and modification. Yet both these investigators continually maintained that their formulations were preliminary and incomplete. Both recognized that

* Presented in part at the Round Table Dinner Meeting of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY, American Psychiatric Association, Chicago, Ill., May, 1956.

neither the etiology nor the pathogenesis had yet been exposed. They believed that a truly adequate system of diagnostics and therapeutics in psychiatry had to rest upon the normal and pathologic physiology of the patient. The year 1956 has clearly marked a turn toward biologic psychiatry and as such represents a fitting creative and productive memorial to both Freud and Kraepelin.

At least two major areas of investigation embrace the research activities of what should be termed psychobiology.* One involves the attempt to elucidate disordered mechanisms that lead to psychotic or deviant behavior by means of the induction of "model" neuroses and psychoses. This method is represented by the expansion of research on the pharmacologic and metabolic agents that may induce facsimiles in presumably normal persons of certain of the phenomena present in psychotic patients. The second area of research centers upon treatment of mental disorders and is represented by the attempt to find new therapeutic agents and to determine the reasons for their effectiveness. The major portion of the articles in the symposia presented in this issue are devoted to one or the other of these problems.

Research, like an avalanche, may tend to develop independent momentum and to be so self-concerned as to lose broad scientific and clinical perspective. Problems can spring not from psychiatry itself but from the operational details of specific research. One antidote for such constriction is historical perspective, that is, the ability to understand present activity within the framework of the totality of past experience and to define current concepts in their relation to the contemporary social and scientific environment. Consequently, it is appropriate at this time (1) to examine the roots of this new psychobiologic viewpoint in terms of the immediate and distant past; (2) to integrate the present day therapeutic and research efforts with that which has already been established; and (3) to scientifically and imaginatively develop perspectives for a future, which, at the International Congress of Psychiatry in 1950 and at the American Psychiatric Association in 1949, van Ophuijsen and his co-workers referred to as the era of metabolic psychiatry.

PSYCHOLOGIC HERITAGE

The roots of psychobiology and their nourishment over the past decades are ably presented elsewhere in this issue. Here we would like to emphasize that their sustenance to the present was provided in the main by French, Swiss, and British psychiatrists, a true fulfillment of a rich biologic heritage.

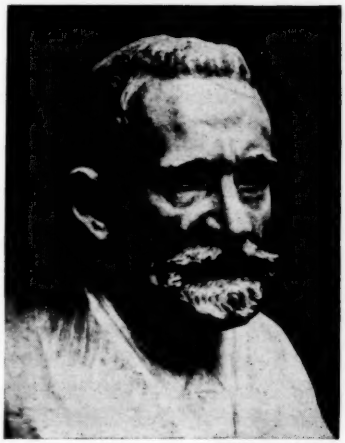
It is important to note that historically the so-called ataraxics and antitensive drugs, i.e., the phenothiazines, reserpine, and meprobamate, were preceded by (1) convulsive therapy, such as electric convulsive therapy (Cerletti) and metrazol (Meduna); (2) insulin coma

* Psychobiology has for historical reasons come to be associated with a particular psychiatric viewpoint, namely, that of Adolph Meyer. It is, however, undesirable to continue such a delimitation of nomenclature, and we believe that the term psychobiology should be expanded to designate the totality of effort being exerted to establish psychiatry based on biology. It is in this new sense that the term psychobiology is used in this issue. Psychobiology, in our estimation, is a concept or philosophic viewpoint of the entire field of psychiatry rather than the theory of a given school.

therapy (Sakel) and subcoma therapy (Polatin and Bennett and Miller); (3) artificial hibernation or prolonged sleep therapy (Klaesi); (4) hormonal therapy, such as thyroid (Kraepelin,[1] Gjessing,[2] Danziger,[3] Hoskins,[4] Reiss,[5] and Sackler[6]), sex hormones, in the main testosterone (Hoskins,[4] Sackler,[7] Altschule[8]), and desoxycorticosterone acetate (Jens); (5) acetylcholine (Fiamberti[9]); and (6) histamine (Hill,[10] Sackler,[11] Rouleau and Nadeau[12]).

The common denominator of these prior therapies, with the exception of electric convulsive therapy and prolonged sleep, was that physiologic or biochemical substances were employed; therefore, previously they have been termed biochemotherapies. The use of biochemical substances gives the researcher a certain advantage, for, if the psychoses are the result of one or more metabolic dysfunctions or dysequilibria, the employment of biochemotherapy may in the long run be more effective and less harmful than nonphysiologic agents. Furthermore, the use of biologic agents in therapy may also provide information that will more fully enhance our understanding of the physiologic mechanisms that constitute the disease.

Certain of these prior therapies, which have also been called physiodynamic since they induce alterations in metabolic parameters, may not have had the dramatic influence on behavioral manifestations that results from administration of the ataraxics. However, they did exert a significant influence on the disease processes encompassed by the term schizophrenia. It is also possible that they could have effected an even more significant effect than was actually observed as, for the most part, administration was rarely continued for more than four to eight weeks, a duration of therapy that does not begin to approximate the six months to one year employed with chlorpromazine and reserpine.



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EMIL KRAEPELIN
(1856–1926)

Fortunately the advent of the newer drugs enabled us to maintain orally administered medication over indefinite periods. This was a welcome fulfillment of some of the hopes of those who over the years insisted on a metabolic orientation, particularly in the study of the functional psychoses. However, these substances, despite their admitted usefulness, are not the ultimate in therapy and as yet have not furthered our understanding of the disease. Rather, their widespread utilization raises new questions for investigation and provides expanded opportunities for research.

RESEARCH ORIENTATION

Unless our perspective is broadened and our philosophy strengthened, the present day therapeutic practices carry within themselves a threat to the continuing development of scientific psychobiology and of metabolic psychiatry. If researchers become engrossed in

clinical therapeutic evaluation of new agents and neglect adequate study of the why of the beneficial effect, we shall be in the position of being led by pharmacologists and biochemists instead of giving our own leadership.

We can either sit back and accept the concept of tranquilization or ataraxia as an answer or we can come to grips with the challenge: Is the drug interfering with a pathologic metabolic state? What tests must be employed to establish the existence of this state? What steps must be planned to sharpen our observation of therapeutic effects? What new clues do these agents give us, if any, in the search for etiologic and pathogenetic mechanisms?

Methods are available for answering these questions, and newer techniques are constantly being forged. It is worthwhile to examine some recent studies that suggest methods and concepts that may be useful.

Co Tui,[13] at the Creedmoor Institute, noted that in patients receiving chlorpromazine over a varying period a significant fall in blood levels of 17, 21 dihydroxy-20-ketosteroid was demonstrated, whereas in patients receiving reserpine this parameter of adrenocortical output either did not change or induced a slight increase. This observation is extremely interesting in view of clinical reports that indicate that chlorpromazine is far more effective than reserpine. And certainly chlorpromazine is recognized as having the power to induce more rapid benefits.

Reiss[14] (Bristol, England) reports that rats, after only four days of chlorpromazine, showed a decrease in weight of the thyroid gland, an increase in radioactive iodine uptake, an increase in weight of the adrenal cortex, and a decrease in the size of the ovary. One injection of chlorpromazine caused a significant increase in the ACTH content of the anterior pituitary. Unfortunately this preliminary report does not present data on endocrinologic effects when the drug is administered over a long period. However, Reiss did note that, while a single treatment with electric convulsive therapy was associated with a drop in radioactive iodine uptake (in both intact and hypophysectomized animals), 24 hours later there was an increase in uptake. Furthermore, daily electric convulsive therapy (more closely approximating its clinical use) induced depression of ACTH content of the pituitary and elevation of the thyroid stimulating hormone level. Similarly, while a single insulin coma was followed by three days of increased ACTH content in the pituitary, after the fourth day a decrease in this level was noted.

HISTAMINE AND TESTOSTERONE

It is also contributive to examine briefly some additional new work with the older biochemotherapeutic substances that preceded the ataraxics. In a recent detailed report on the use of histamines in 100 hospitalized schizophrenic patients, Rouleau and Nadeau[12] confirmed earlier reports of its beneficial effect. After only four weeks of treatment, which was a rigid criterion established at the Creedmoor Institute when evaluating new therapies, 20 of the patients improved sufficiently to permit them to be discharged from the hospital. Interestingly enough, of the remaining 80, 76 were given electric convulsive therapy, and only one remission resulted. However, when the remaining four patients were given electric con-

vulsive therapy with thyroid, three showed improvement. But of more basic importance was the study of the effect of histamine on insulin tolerance.*

The Canadian workers report that many schizophrenics (approximately 60 per cent) show delayed or decreased sensitivity to insulin and a reduced response to the insulin-induced hypoglycemia after repeated testings. The influence of the anterior pituitary and of the adrenal glands upon the hypoglycemic effect of insulin and upon the restoration of the blood level is established. In fact, Gellhorn[15] maintains that the adrenocortical hormones are mobilized even in adrenodemedullated rats.

Normal sensitivity to insulin as measured by the test can be restored by intravenous administration of 25 Gm. of glucose given prior to the insulin (glucose-insulin tolerance test of Lazarus and Volk). Rouleau and Nadeau believe that hyperglycemia inhibits or reduces secretion of insulin antagonists, which, if increased in psychosis, would be reflected as insensitivity to insulin.

Clinical improvement after only four weeks of histamine therapy was associated with metabolic changes indicating homeostatic readjustment during what appeared to be a phase of adrenocortical hyperactivity. Of the 41 patients tested, in all seven who showed clinical improvement increased sensitivity to insulin was demonstrated after therapy, although sensitivity had been decreased before. Five of the group of improved patients also showed hypoglycemia, although responsiveness had been increased before treatment.

Rouleau and Nadeau concluded from this that "Adrenocortical hyperactivity, being consistent with decreased sensitivity to insulin and increased responsiveness to hypoglycemia, appears to condition the effectiveness of histamine as a biochemotherapeutic agent."

Hoffer and Parsons[16] also reported beneficial results in 9 of 12 patients so treated, with 3 maintaining improvement, although therapy was limited to four weeks. Lucy[17] confirmed the extremely high tolerance to histamine in schizophrenic patients, a tolerance that was associated with severity of psychosis.

Attention has been directed to these reports, not only because of an ill-concealed prejudice in regard to biochemotherapy but, more significantly, because they underline a philosophic viewpoint that is important. Therapy is of significant benefit to the psychotic patient when and only when it induces metabolic changes or interrupts pathophysiologic processes. The search for the why of the action of any beneficial agent will help us uncover the why of the disease process.

In 1950 we reported[7] the beneficial effect of sex steroid therapy (testosterone and estradiol), that is, the convalescent status achieved by 30 per cent of 40 state hospitalized schizophrenic patients after only four weeks of treatment. Since then the value of this combination of hormones has been accepted in general practice as being of benefit in geriatric patients, and

* In previous reports we have shown (1) the extremely high tolerance to histamine (also to thyroid hormone) exhibited by the schizophrenic patient; (2) the influence of histamine on glucose metabolism as recorded in the glucose tolerance test; (3) the influence of testosterone on the glucose metabolism of schizophrenic patients, and the association of clinical improvement with more normal findings in this area, as well as with a marked eosinophilia, which we attributed to reduced sympatheticoadrenocortical activity.

the value of testosterone had been attested to in the treatment of schizophrenic persons by Altschule,[8] Reiss,[18] and Sands.[19] Sands, too, has found that testosterone improved adolescent patients who were emotionally, socially, physically, and biochemically immature.

The association of clinical improvement following therapy with testosterone with a marked eosinophilia, a phenomenon also noted after spontaneous remission and after insulin therapy, has been interpreted as indicative of relatively depressed sympatheticoadrenal function when remission of schizophrenia has occurred.

THYROID HORMONE

The importance of thyroid hormone as an aid in the correction of hormonal dysequilibria in schizophrenic persons is emphasized by Reiss. As already mentioned, daily electric convulsive therapy induced a drop in pituitary ACTH content and a rise in thyroid stimulating hormone content.

Robinson,[20] in his research, reported an interesting observation on patients with hyperactivity of the thyroid and psychiatric symptomatology. He emphasized that often these patients show evidence of failure to utilize endogenous thyroid and testosterone at the peripheral level. Uptake of radioactive iodine is increased but the basal metabolic rate is often low—a dissociation of function.

Sands makes interesting use of thyroid function tests for prognostication. He notes that with decreased or normal thyroid-tracer results in the presence of increased 17-ketosteroid excretion, the prognosis is good for insulin coma, and that with increased or decreased thyroid-tracer in the presence of decreased 17-ketosteroid excretion, the prognosis is poor for insulin coma. These patients are of the type referred to by Robinson as often showing failure of hormonal effect at the peripheral level; he has utilized niacin to good effect in such instances. Sands has employed low dosage testosterone with beneficial results when both thyroid function and steroid excretion were low. Decreased thyroid function with normal ketosteroid excretion often responds to administration of thyroid. Normal thyroid function and depressed 17-ketosteroid excretion has been used by Sands as an indication for high doses of testosterone.

Sands also comments that clinical improvement is generally accompanied by decreased 17-ketosteroid excretion for the duration of therapy.

PROGESTERONE

Progesterone has been employed for postpartum psychosis by Bower and Altschule[21] in doses of 100 mg. daily given intramuscularly for 10 days, then 150 mg. given orally for maintenance. They utilized massive doses not available to us at Creedmoor in 1949, at which time we reported on the beneficial results attained on a small group of postpartum psychotic persons. With larger doses Bower and Altschule noted that in practically all of 16 patients, who had suffered a relapse after beneficial therapeutic results by other means, a remission maintained.

From the afore-mentioned data it can be seen that the common major effect of the benefi-

cial agents known to date seems to be an antisympatheticoadrenal action. In the light of this background, it would appear that the ataraxics must be viewed as more than mere tranquilizers. From this perspective, research logically would then attempt to define the metabolic state that is present during a psychotic episode and the influence upon this physiologic substrate by the drug being studied. The directions of action, their depth, and their significance have yet to be elucidated.

RESEARCH PROBLEMS

It is to be hoped that this survey has clarified to some degree several of the biochemical areas that link the old with the new. The exciting work with drugs that induce psychotic-like states, the uncovering of physiologic substances or derivatives that induce psychotic phenomenon, the search for the why of the action of beneficial drugs, and the discovery of the etiologic and pathogenetic mechanisms underlying the so-called functional psychoses—to mention a few of the research tasks ahead—are a challenge which will require effective organization of much of psychiatry's resources.

Researchers will learn from the pitfalls encountered in the neuroendocrine studies of the past, for, in these earlier studies, confusion arose because of methodologic inadequacy. Such inadequacies included the following.

1. The time patterns are different, that is, one day of therapy need not necessarily induce the same changes found after a course of therapy. Furthermore, even with one dose of an agent there may be a diphasic response, thus requiring continued observation over a period of time.

2. The concentration of interacting elements into which a therapeutic agent is introduced is different in different persons at different points in time of the disease process. This may lead to varying therapeutic results and confusion in interpretation. Biochemical spectra of various key functions may be the answer to this problem. The British utilization of two parameters determined at relatively the same point in time, namely, iodine uptake and 17-ketosteroid excretion, is a step in the right direction in our opinion. Furthermore, proper distinction between tests of actual function and tests of reserve function must be made.

3. That physiology is constantly dynamic and that changing can continue to be an obstacle to progress was not employed or taken into account. Physiodynamics, the antagonistic-synergistic relationship of hormones, enzymes and other biochemical and even molecular substances, must be kept constantly in mind. It is not only pituitary-adrenal or pituitary-thyroid; it is the entire endocrinium in functioning balance, each hormone with the other and under the influence of other biochemical substances.*

4. Planes of function or the range of equilibria may vary in different persons. We may detect abnormal levels of any one element in either direction. By itself this is of little value, for the entire equilibrium may have shifted uniformly in the same direction. Or a normal

* The very word homeostasis would be better replaced by the term dynamic equilibria for functional states accepted as normal and by dysequilibria for states associated with psychologic or biologic aberrations.

level of one parameter may be found, and the others may have shifted to a different plane inducing a relative hyper- or hypoactive state.

5. Finally, the sensitivity of the end organ, in this case the brain, may be a determinant to the onset of psychosis. Here heredity, congenital effects, developmental patterns, and external environment exert their influence and may help explain why some patients with similar biochemical dysfunctions may show evidence of psychosis in childhood, why some may show it during puberty, some postpartum, some during adulthood, and some in senility.

Psychobiology can now begin to encompass the full scope of biologic and psychologic psychiatry in an integrated, interacting totality. Advances in clinical psychiatry may include, for example, (1) elucidation of the pathobiography of psychosis; (2) recognition of that large segment of the population that is physiologically preschizophrenic or has compensated latent schizophrenia; (3) delineation of the childhood psychoses, especially schizophrenia; (4) development and integration into research and practice of improved psychologic procedures; and (5) utilization of clinical research teams that will include the biochemist, the physiologist, the geneticist, and the epidemiologist, as well as the present group of psychiatrist, psychologist, social worker, and nurse.

These advances will help us to bring closer the day of preventive psychiatry, the day when we will be able to afford our people the right to protection against mental illness as another of man's inherent rights.

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What is Psychobiology Today?*

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HISTORICAL BACKGROUND

Psychobiology today is the lineal descendant and beneficiary of great men of divergent views and of a series of different schools with conflicting concepts. Pinel, in 1793, physically and symbolically struck the first blow to remove the physical and psychologic chains that isolated the psychiatric patient from his social community and psychiatry from the medical community. He gave us the first in a series of contributions of the French school of psychiatrists. His countrymen, in seeking to portray the clinical pictures of psychopathology, were among the earliest to advance psychiatry in the direction of a science. Significantly, it was Bernheim, Professor of Clinical Medicine at the University of Nancy in France, who was credited with first using the word "psychobiology" in 1886. Psychiatry then leaped the Franco-German border to benefit from the nosologic contributions of Kraepelin who at the turn of this century sought to organize the data of clinical observation in his historic attempt at classification. Kraepelinian nosology was another definitive step in the direction of a scientific psychiatry. Its limitations were recognized by Kraepelin because he was among the first to sense, because he did not have available data to do more than that, a possible connection between dementia praecox and neuroendocrine function.

Then from Vienna came the contributions of Freud as he probed, postulated, and popularized the psychodynamics of symptom formation. The Englishmen, Jackson and Sherrington, and the Russian, Pavlov, brought into focus the realization that the functional integration of the elements of the nervous system is also a legitimate province of those who sought the answer to the diseases of the mind, even as the Spaniard, Cajal, gave us new weapons for better understanding of some of the components of that system. Then, Swiss by birth and American by choice, Adolf Meyer, with whose name the word "psychobiology" has become so intimately associated, sought a sounder scientific foundation for this descendant of the humanity of philosophy and made it a more humane and sounder science by properly stressing the biographic, endogenous, and social influences upon the psychiatric patient.

Fortunately, metabolic processes recognize no religious, political, or nationalistic creed, and so, psychobiology has outgrown and towers above the warring factions of Kraepelinians who out-Kraepelin Kraepelin, Pavlovians who out-Pavlov Pavlov, Freudians who out-Freud Freud, and Meyerians who out-Meyer Meyer.

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DEFINITION

Psychobiology, as we conceive it today, is the scientific discipline that seeks to study the physiologic, metabolic, or biochemical processes that cause and/or mediate and/or are reactions to ultimately classifiable mental and emotional disorders of a historical organism existing in time and functioning in an external social and physical environment and an internal physiologic and psychologic milieu.

The psychobiologic approach to psychiatry should seek to use the best of the techniques, knowledge, theories, matériel, and instruments of the physical sciences to define and to understand and to control and to correct psychologic aberrations occurring in a biologic entity. Psychobiology today, though etymologically derived from the psychobiology of Meyer, is more than a Bernheimian or Meyerian psychiatry. For Meyerians it was a more literal translation of its Greek roots—a study of the psychology of the life of the patient—perhaps more a psychobiography. Psychobiology today is closer to the biologic and physical sciences and further from its humanistic and primarily philosophic origins as a social science. As it becomes more firmly rooted in physical facts, it will closely approach the ideals of a pure physical science.

RELATIONSHIP TO PSYCHOBIOLOGIC ANTECEDENTS

What is the relationship of modern psychobiology to its antecedents? (1) It accepts the fundamental principle of the importance of Kraepelin's nosology without predicating all upon the Kraepelinian classification. (2) It can accept only as working hypotheses some of the Freudian formulations as to symptom formation even as it must deny that the psychodynamics of symptom formation can be arbitrarily equated in all disorders with etiology or with pathogenesis. (3) It accepts as a fundamental fact that the physiologic processes demonstrated by Sherrington and Pavlov may prove essential to our understanding of some aspects of psychiatric processes without accepting the point of view that they may be the only basis thereof. (4) It accepts Meyer's psychobiographic contributions and his recognition of the psychiatric patient as a social unit without necessarily considering his reaction types as indispensable.

In a phrase, psychobiology accepts the substance of the principles of much that these men fought for but rejects the contentions and efforts of their followers to have Freudian psychology, Meyerian reaction types, or Pavlovian physiology displace or take the place of all clinical psychiatry. They are parts of clinical psychiatry and *not* the sum total of the science of psychiatry.

CONTROLS

What are the controls that psychobiology must submit to? (1) Psychobiology must submit to the fundamental precepts of every scientific discipline, that of the experimental test, the objective collection of sufficient facts under suitable safeguards to assure their validity. (2) Even as psychobiology must seek theoretic formulations, it must clearly

differentiate between an objectively defined fact and a derivative postulate or a hypothesis. (3) Psychobiology must accept as a premise Claude Bernard's injunction that the relationship between cause and effect is the fundament of any science and that when such is defined it must be susceptible of proof and, wherever possible, counterproof. (4) Psychobiology must be rooted in clinical psychiatry for, as van Ophuijsen put it, "Research in this field should accept the guidance and conditions imposed by the knowledge of clinical facts if it does not want to go astray as did psychoanalysis whenever it refused to accept this control." Psychobiology has also gone astray when it flies in the face of clinical fact, as when adrenocortical deficit was implied in a clinical condition, some of whose victims could demonstrate the proverbial strength of a "madman."

TASKS

What are the tasks that confront psychobiology today? (1) It must "quantitate," that is, it must provide specific criteria and procedures for the objective measurement of symptoms and other manifestations of psychiatric disorders, objective measurements for the definition of diagnoses, and objective measurements for evaluation of clinical response to therapeutic measures. (2) It must seek out, "isolate," and define those physiologic mechanisms—the metabolic, biochemical or biophysical processes—that are involved in the etiology and pathogenesis of psychiatric disorders; that mediate psychogenic and somagenic psychiatric factors, and that are reactions to these factors. (3) It must create an etiologic nosology upon which ultimately specific metabolic, as well as other pharmacologic, measures of therapy can be based. (4) It must, as do all of the physical sciences, relate the data derived from experiment in order to seek general biologic laws that will confer in the field of psychiatry a suitable measure of predictability and, through predictability, control of the phenomenology of psychiatric disorders.

MEASURES AND PROCEDURES

What about some of the measures and procedures that psychobiology must use? First, it must use every modality of science, theory as well as experiment. One such theoretic instrument that has been proposed is part of the title of this round table. It speaks of a physiodynamic psychiatry. Our physiodynamic formulations conceive of this biologic-psychiatric science as founded upon an extremely dynamic physiology in which are recognized (a) time patterning of biologic processes, (b) the influence of the operation of multiple opposing forces or antidynes on all biologic parameters and equilibriums, and (c) the differentiation between absolute, relative, and operative concentration of physiologic forces (among other factors).

In using scientific theory, psychobiology must emulate the theoretic boldness of physics and mathematics. In the American biologic sciences, and more particularly in the medical sciences, one finds a sensitivity reaction against theory amounting virtually to "anaphylaxis." While those so sensitized attribute their approach to theory to the need for "a more

objective approach," the facts are that there is a difference between true scientific doubt and simple cynicism. Claude Bernard was clear in this differentiation and in his warning against the antiscientific nature of cynicism. The fear of theory, and the failure to use it, is probably related to the failure to comprehend its function.

Theory is one of the highest functions of science, for it grows out of the correlation of scientific facts and provides an indispensable instrument for the discovery of new facts, as it facilitates and gives direction to the formulation of new experiments and is subjected to their test.

The critical attribute of predictability, a phenomenon that is inherent in good theory and in all general biologic and physical laws, advances the acquisition of newer knowledge, enabling modification and refinement of theory.

A scientific theory always serves an important scientific function, for we conceive it in order to better understand the data from which it is derived; it leads to the discovery of new facts through the application of its principles and through the experimental tests through which we put it. And then, when it no longer yields new knowledge through these measures, it is the obligation of both those who conceived of these theories and those who utilized them to destroy it by further experiment, for, in the destruction of a theory, the theory serves again its primary function of gaining a better understanding of the facts at hand and acquiring new facts; out of the destruction of such a theory comes new and more advanced theory.

Lest it appear that these are merely glittering generalities, may we note that the physiodynamic approach to psychobiology had been able to bring to our young science a significant measure of predictability despite the imperfections that are inherent in any theory, particularly in a newly formulated one. Between 1948 to 1950 it enabled the prediction that cortisone and ACTH would produce psychoses in certain individuals and yet might be of benefit in psychosomatic disorders. The correctness of certain of these predictions is a matter of record. Then in 1949 and 1950 it suggested on theoretic grounds that the use of gonadal hormones in postpartum psychoses should prove beneficial. Bower and Altschule's recent paper[1] in which they demonstrated clearing of postpartum psychoses with progesterone provides fascinating corroboration of this prognostication. That same year the high incidence of hirsutism, and the low incidence of peptic ulcer and asthma during hospitalization for psychoses, was referred to (together with other data) as indications of adrenal imbalance in schizophrenia. Lea's report on adrenochrome[2] and Hoffer's work are interesting commentaries on this hypothesis. Adrenal medullar excess was also hypothecated to be related to anxiety and manic-depressive psychosis (depressed phase). Funkenstein's experiments and his remarks at the Biologic Society meeting bear an interesting relationship to this.

It was proposed that the complexity of cerebral processes was such that among other possibilities an interference in the tricarboxylic cycle at isocitrate or pyruvate could be one of a score of different mechanisms involved. Clark's comments at the Biologic Society meeting on the importance of further studies of pyruvate and phosphate metabolism show that these possibilities are today not being overlooked.

The utility of such formulations carries beyond psychiatry and the physiodynamic approach, for they enabled the definition of a previously unreported function of the thymus gland. Based upon such biologic grounds, a quantitative diagnostic test was then conceived as possible, and, following a brief trial by phytoassay of a rose, similar to Macht's earlier work, it was demonstrated that changes in the physical characteristics of blood could be utilized to differentiate between psychotic and nonpsychotic persons. This, too, is interesting in the light of Hoffer's report at the Biologic Society meeting.

Second, in regard to other measures and procedures that may be used, biochemotherapeutic studies can make a double contribution to psychobiology. We have defined biochemotherapeutics as the therapeutic utilization of physiologic substances. The reason their contribution is greater is that they not only provide therapeutic opportunities but also focus research on physiologic mechanisms and metabolic processes. Being physiologic elements, they are one step less removed from metabolic processes than are pharmacologic agents. Because of the wide range of such substances, they stress the probable metabolic complexity of the states we study, even though they are today grouped under single headings, such as the schizophrenias. Furthermore, the chronicity of the disorders we study warns against the illusory prospects of a single simple solution, minimizes the prospect that therapy can be brief, and also requires us to think in terms of correction before we can think in terms of cure.

The biochemotherapeutic approach must also be rooted in clinical psychiatry, for it is a fact that the mechanisms and processes involved in psychopathology are corporeal functions and that, when a psychiatric disorder goes into "spontaneous remission," psychopathology has been "corrected" through physiologic mechanisms and processes.

Third, the pharmacodynamic approach affords vital opportunities, for example, the so-called tranquilizing agents, if they are studied pharmacologically and physiodynamically, can give us valuable insights into physiopathology even as they, through their current popularity, spare thousands of patients the irreversible psychosurgery and preserve them for psychobiologic benefits yet to be discovered. The psychoses-inducing agents also have an obvious contribution to make in presenting opportunities for controlled experiment and, by virtue of their multiplicity, in pointing out that psychopathology may be arrived at by varying physiologic and metabolic pathways.

CONCLUSION

It was at the First World Congress of Psychiatry in Paris in 1950 that we reported, "We must record that out of our findings has come the conviction that we are today on the threshold of metabolic medicine and metabolic psychiatry. . . . We have upon this occasion (tonight) presented in more specific terms some of the controls, disciplines, tasks and opportunities which confront a psychobiologic psychiatry.

"Today we heard a most scholarly academic lecture on 'The Great Psychiatric Revolution.' Those of us whose heads were bloodied on the psychobiologic barricades raised during the 1940s could well have used such support in those days. On those scientific barricades there

were but few men but they were good. Johan H. W. van Ophuijsen, who fought in the Freudian psychiatric revolution, was a leader again in the psychobiologic revolution. Meduna was there. Braceland gave of his help generously and wholeheartedly. Overholzer provided inspiration and facilities to Katzenelbogen and Winifred Ashbey. There were the efforts of Malamud, Himwich, Hoagland, Pincus, Altschule, Hoskins, Reiss, Rinkel and Funkenstein, the Creedmoor group, and a handful of others.

Though the "purge" which was administered this morning was long overdue and needed, we nonetheless believe that there have been psychiatric revolutions and that we are in the midst of one today. I have at this time sought to portray for you the terrain upon which a number of leaders in the new revolution of psychobiology, who are with us tonight, will engage their minds. The component sections of this report have served to briefly introduce and to integrate the component elements of the meeting tonight. A great medical historian will place psychobiology in its perspective; a physiologist and theoretician will utilize theoretical formulations as his contribution; a pioneer psychobiologist and psychiatric clinician will talk about the problems of quantitating symptomology and clarifying its nosology; a leader in psychiatric education, administration and clinical psychiatry will relate some of the recent advances to the management of hospitalized patients; a young and imaginative researcher will seek to tackle some of the unique problems that psychobiology faces as an experimental science; a pioneer in pharmacopsychiatry will bring us something of his own experience and represent for us the truly glorious scientific traditions of France—not only of the psychiatry of Pinel, Esquirol, Janet and Bernheim, but also of the outstanding work of our contemporary French colleagues; and lastly, one of the newer endocrinologic concepts will be reviewed in relation to the perspectives and opportunities which face modern psychobiology.

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Ars Medica

Eighty-five prints representing the teaching and practice of medicine were exhibited during the month of October at the New York Academy of Medicine. The collection is entitled *Ars Medica*, or the Healing Arts, and is owned by the Philadelphia Museum of Art.

The prints, assembled into 15 panels depicting the various phases of medical history and practice, were included in the collection for both their artistic quality and their medicohistorical value. Artists and illustrators, such as Bruegel, Daumier, Goya, Hogarth, Holbein, Kollwitz, Lautrec, Rembrandt, Steen, and Wechtlin, are represented; some of the prints are well known, others are rare.

The Historical and Philosophic Background of Psychobiology*

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THE HORIZON OF PSYCHOBIOLOGY IN 1956

What three great contributions can psychobiology make in our time?

First, the philosophic integration of psyche and soma not only in psychosomatic medicine but also in clinical psychiatry, and in both cases in etiologic research and diagnosis.

Second, inclusion in the clinical history of the element of time, the *biographic* component, basic in anamnesis and of vital importance in prognosis.

Third, the introduction of biochemical and chemotherapeutic agents in solving etiologic, diagnostic, and therapeutic problems in psychiatry.

Psychobiology, as a new trend in psychiatric investigation and as a happy union of three factors in psychiatry—biographic, biologic, and pharmacologic—has challenged the philosophic dictatorship that existed in psychiatry and is investing it with the full dignity and stature of a science.

Psychobiology has also made it possible for psychiatric congresses such as this one to be more scientific, more practical, and more universal than ever before, for it has opened their doors to an enthusiastic and energetic legion of physiologists, chemists, biologists, physicists, and even mathematicians, who can bring enlightenment to psychiatry with their wisdom.

But above all, psychobiology has accomplished an important scientific vindication, it has made it possible for the psychiatrists of state mental hospitals—those forgotten back-bench workers, in fact, the infantry of psychiatry, whose clinical material, the "small change" of psychiatry, has enormous practical and statistical value—to retrieve the place of honor they so richly deserve.

Psychobiology, furthermore, has made it possible for etiology to add to its psychiatric roots metabolic, endocrine, and biologic roots, just as it has made it possible to add the biographic and anthropologic aspects to the nosologic phases of the clinical study of a disease.

All this has made psychiatric diagnosis wider and deeper, although in becoming multi-dimensional it has also become more ambiguous, since we still lack objective criteria to evaluate its components. Prognosis has also gained a social and chronologic dimension, although it still is not given the importance it deserves, probably because of its uncertainty.

Finally, therapy is also moving toward new methods that, although slower, are more lasting than the shock therapies to which the patient's physical integrity is still subjected

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in the haste to cure, a haste that has made both the patient and the psychiatrist stop trying to help nature effect a spontaneous recovery. This haste also explains why we are no longer interested in the metaphysical problems of death that so fascinated psychiatrists in the past century. If today we lack time for living, how can we possibly find time for worrying about death and the hereafter?

Psychobiology has also opened new biologic roads for psychiatric research into the organic changes in schizophrenia: the effects of mescaline and LSD in normal subjects and in mental patients in order to produce "pocket-size" psychosis; the decomposition products of epinephrine in the organism of the schizophrenic; hormonal balance; the alteration of the tricarboxylic cycle in cerebral metabolism; adrenal changes; brain lipoproteins; cerebral circulation and oxygen consumption; and the nervous tissue and its possible hormones. These "classic" brain hormones—the "nervous juice" that already intrigued Spanish physicians, such as Sabuco, in the Spain of Don Quixote—are perhaps the secret of the activity of the pituitary-hypothalamus-adrenal block, that *terra incognita* where the mystery of psychoses may be hidden.

THE SEARCH FOR MENTAL PEACE

What underlies the obsession of twentieth century man to know and to cure mental disease? Down through history each century has had a basic preoccupation that served as a guide to man's activities in that period. In the sixteenth century, man searched for the ideal form in art, just as in the seventeenth century he searched for a philosophy in science. In our century, man searches for mental health and peace of mind.

Half a century ago, the great philosopher Ortega y Gasset, one of the most luminous minds of our time, called ours the "Aspirin Age" because, instead of looking actively for happiness, modern man was satisfied with the modest happiness afforded by a handful of drugs with melancholy names. Ataraxia, peace of mind, has become an obsession with modern man, whose mind is unceasingly being shaken as never before in history by wars, revolutions, and the juggernauts of technical progress.

We have succeeded in reducing the incidence of *accidental* diseases of *external* origin (traumas, infections, intoxications), but, on the other hand, we have witnessed the increase of *personal* diseases of *internal* origin, such as mental, sclerotic, and degenerative diseases. Faced with this new powerful menace, we looked for quick solutions. It therefore became more important to cure than *to know*, which would be acceptable if we could cure without knowing. We accepted therapies of a highly aggressive and even brutal nature, but we neglected the search for the root of things. We created a quick but not a *deep* science.

Fortunately, the pendulum is swinging back again. The necessity to cure led to the yearning to know; this in turn led back to the desire to cure but in a more rational way, for, in science, as in life, the shortest way may be that pointed out by the poet who said: "The shortest way between two points is the one that crosses the path of the stars."

THE PHILOSOPHIC ROOTS OF PSYCHOBIOLOGY

What are the philosophic roots of the current psychobiologic trends in psychiatry? The

history of psychiatry may be summed up by saying that it was 5000 years of demonology and 1000 years of painful groping in the dark for a scientific principle. For over 1000 years it accepted the Hippocratic endeavor to establish a physical cause for mental disease, mania, and melancholia as effects, and the elimination of *materia peccans* as its therapy.

In that historic cycle the therapy and management of mental patients proceeded from the phase of *isolation* of the patient to an *institutional* phase, to the *management* phase induced by Pinel, to the *seismotherapeutic* phase of *shock therapies*, and finally to the phase of the *physiodynamic therapies*.

During the historicophilosophic evolution of psychiatry, the three great goals were: elimination of the symptoms—hallucinations, agitation, and negativism—that made the mental patient "different" from other patients and made his therapy and management difficult; establishment of communication with the patient, isolated as if on a deserted island by the invisible walls of his disease; organization and management of the patient on the same basis as any other disease, that is to say, maintaining the patient's contact with the outer world and hospitalizing him only during the phase of acute paroxysm or extreme chronicity of his disease. To these therapeutic and management objectives has been added the desire *to know*, not by weaving subtle philosophic patterns but by ventilating psychiatry with the clean fresh breeze of a biologic criterion and new technical resources.

As a result of Virchow's theories, up to the end of the past century when scientific psychiatry really began, the microbe reigned as supreme dictator in medicine. Then suddenly something of tremendous historic importance happened: the biologic essence of the patient's life was rediscovered. From a mere thing, the patient became a living *being*. The organic totality and the neurophysiologic and humoral unity of the living body were also rediscovered. In a way, it was a renaissance of the old constitutional pathology—the classic *idiosynkrasia* and *temperies*—and the symptom began to be considered as a response to a biologic situation created in the organism by the disease.

Totality, constitution, and responsiveness became the three new points of view of the psychiatrist, together with the principle that the patient's personality is situated in a certain *environment* at a certain moment of time; that is to say that man is a *social* person but he is also a *historical* person. The psychiatrist, and later the physician, was suddenly faced with a new unknown country to explore: the *total person* of the patient.

From the old Galenic concept of disease as a passive affliction, the psychiatrist passed to the Sydenhamian concept of disease as an active effect of nature intended to cure man. Disease became then an abnormal and painful way of life, but still *a way of life*.

THE GIANTS OF PSYCHOBIOLOGY

Cajal, Pavlov, Sherrington, Kraepelin, Bleuler, Freud, and Meyer—these men laid the foundations of the psychobiologic revolution in the concept not only of mental disease but of disease in general. By a striking coincidence, they were all born in a period of 17 years (1849–1866), the most outstanding in the history of psychiatry for the number of geniuses it produced. Also, in this same period were born Adler, Jung, and others.

Cajal established the anatomic basis and Pavlov the physiologic basis of psychiatry; Sherrington introduced the concept of integration, supplementing the classic concept of evolution and dissolution of John Hughlings Jackson; and, later, Freud introduced the concept of regression and Bleuler autism and introversion. All of these were concepts of the greatest neuropsychiatric importance. Kraepelin converted into a cosmos the nosologic chaos of psychiatry. Under his commanding voice, psychiatric symptoms and syndromes aligned themselves like well-disciplined soldiers into his rigid imperial Prussian army of nosologic entities. Thanks to Kraepelin, systematization in psychiatric methodology and nosology was achieved.

FREUD AND ANAMNESIS

Chronologically, Freud was a contemporary of Kraepelin. Conceptually, Freud belonged to a new generation that was not to be satisfied with merely classifying mental diseases as the entomologist pins down butterflies in his specimen box.

Freud's centennial is now being commemorated not only by psychiatrists but also by other men of science the world over, for Freudian psychoanalysts do not have a monopoly on the man who today would probably be less "Freudian" than they are.

Freud converted pathography into biography, incorporated the disease of man into medical pathology, and considered the sick man as a *man*, thus starting the trend in psychiatry toward a biologic anthropology.

In the line of mankind that goes from the ameba to God, the mission of genius is to unveil a new fragment of the universe and to formulate objective truths. Freud created a psychologic image of man, and as a result man's image will never again be what it was before Freud, just as the images of the universe and the living being will never again be what they were before Galileo and Darwin.

Freud was above all a biologist, and as such he studied mental diseases using biologic methods. His work culminated in the creation of a biologic psychiatry.

The Freudian concept of anamnesis actually resurrected the ancient Assyrian ritual of studying not only the disease but also the biography of the patient. In contrast to the etiologic and pathophysiologic concept of the neuroses prevalent in his time, the great physician of the Berggasse demonstrated the extreme need for the dialogue with the patient. He thus transformed mental pathology from a visual science, as it was with Charcot, to an auditive science. Charcot *saw* neuroses; Freud *heard* them. Charcot dramatized neuroses; Freud practiced "auscultation" of the patient's monologues with the same loving interest with which Laënnec auscultated the chests of his patients for râles.

Freud was an "auditive" type. Even when he wrote he was actually speaking, and when we read him today we are listening to his voice. For Freud each word was an iridescent bubble charged with intimate meanings, a delicate mold imprisoning an emotion.

It was given to Freud to establish the value of the instinctive component in human life, to demonstrate the different modes of consciousness and the influence of the psyche upon the body, as well as the comprehensive, orderly integration into the biography of the patient of the event of disease. Freud began by studying man from the point of view of the natural

sciences and pure biology and finished by having the patient accepted as a person and psychiatry as an anthropologic science.

To explore the dark region of the patient's instincts, Freud used that subtle instrument, the dialogue, a new version of the old anamnesis. The difference was that the traditional anamnesic dialogue was purely descriptive. The patient spoke as a witness or as a spectator of himself and his environment, whereas Freud invited the patient to be an *interpreter* of himself. Afterward he taught psychiatrists to interpret the interpretation.

All this was not completely new. In his "Charmides" Plato mentioned cathartic rituals of a verbal nature. However, since Freud's discovery of the priceless tool of anamnesic dialogue, the psychiatrist has been able to explore the complex etiologic, semeiologic, and configurational interrelationship between the body and the mind of the patient, between his intimate nature and his environmental reality.

In spite of all the opposition, Freud illuminated psychiatry with his concepts. As Cajal once said, "Geniuses, like abyssal creatures, move on illuminated by their own inner light."

MEYER AND PSYCHOBIOLOGY

The work of Freud coincided chronologically, although somewhat preceding it, with that of Adolf Meyer, the originator of the term psychobiology, that incandescent word whose glow illuminates this round table.

Although Meyer was Swiss, he was responsible for the definitive split between American and European psychiatry. In spite of his being a foreigner, he was ultimately incorporated into the life of this nation, just as the Greek El Greco was incorporated into the Spain of Philip II.

When Meyer came to this country two principles prevailed in European psychiatry: *nosologism*, which considered mental diseases as mere nosologic entities no different than any other disease, and *somaticism*, which accepted the concept that mental diseases had organic bases, specifically encephalic, according to the dominant thesis of Griesinger.

Meyer rebelled against the patterning of psychiatry after medicine and the idolatrous cult of diagnosis. The fact that Meyer resided in this country saved him from being overwhelmed by the weight of historical tradition. In this country the past does not weigh on the present as heavily as in Europe, which makes it easier to become emancipated from it since one is not so grateful to it.

Meyer created a psychiatry of common sense which he called *psychobiology* and converted mental disease from an abstract nosologic entity to the flesh and blood reality of the mental patient.

Meyer created a mental pathology based on individualistic principles and resurrected the Hippocratic concept of treating *patients* rather than diseases, thus replacing the nosologic by the personal. Disease for him was a chapter in the biographic-psychobiologic evolution of the individual. By accepting the common root of pathology and physiology in human life, he eliminated the distance then existing between the "normal" man and the mental patient. He rejected the point of view that the brain rather than the personality is more

interesting in the mental patient, and he demonstrated that in the normal or in the sick person this personality must be understood in its constant interaction with the environment.

At the time that Freud was invited by Clark University to deliver a series of lectures (1909), Meyer's ideas had already developed in the United States. The Freudian concept of symptom and disease as defensive manifestations of the individual against the pressures of life helped to shape the concepts of Meyer. And when Meyer's wife began to visit patients' homes with the purpose of investigating their sociobiologic environment, there was started what later became the profession of psychiatric social work.

Meyer created new objectives for psychiatry by concentrating not on the disease but on the patient. First he enlisted neurotics, and then normal persons, in the movement of mental hygiene founded by Clifford Beers. By using psychiatry to teach civilized man how to live, he completed the "Americanization" of psychiatry and gave new impetus to the cultural anthropology originated by Freud.

American psychiatry was then transformed not only by the psychiatrists but also by the patients themselves and by public opinion. Meyer converted psychiatry into one of man's basic sciences by stimulating mental hygiene and psychiatric social work and by enlarging the scope of clinical psychology and psychosomatic medicine. He even tried to study the prevention of war by analyzing the psychologic factors responsible for human aggression.

Meyer was fascinated above all by psychoses, as Freud had been by neuroses. His concept of the personality that pantingly hides in the entangled bushes of a psychosis permeates all modern psychopathology, just as his other ideas have replaced Kraepelinian psychiatry.

When Meyer died in 1950, he left a glittering heritage: his concept of the *whole man*. Instead of looking with a magnifying glass at each facet of man, Meyer examined his image as if through a reducing glass, which produces a sharper, clearer image. He attempted to integrate psychology and biology, and he studied the behavior of the whole man as a reaction against environmental stresses, representing in his diagrams the chronologic and the clinical history of the patient's disease. If Kraepelin went from general concepts to individual facts, Meyer reversed this process by replacing the nosologic with the personal.

Meyer's main contributions to psychobiology may be summed up thusly: (1) the concept of disease as a simple chapter in the biographic integral evolution—psychobiologic—of the individual; (2) the integration of the environment and its influences in the study of mental disease, a concept that inspired present-day psychiatric social work; (3) the extension of the province of psychiatry to a study of the "normal" individual, thus stimulating the movement of mental hygiene; and (4) the study of the total personality of the patient and not merely the nosology of the disease.

PSYCHOSOMATIC ROOTS

Let us now consider another current of thought, that of psychosomatic medicine, a term that up to 1948 was still written in italics, indicating that it was not accepted "officially."

Psychosomatic medicine was the inevitable historical reaction to the situation that prevailed half a century ago, when the ideas of Johannes Müller and Claude Bernard were still

dominant. The prevalent concept then was that medical pathology was but changed physiology. This confined psychiatry to the laboratory, or at best to the hospital, and prevented the recognition of the *extrasomatic* components—social, historical, and psychologic—of the individual biography until the advent with Freud of the new anthropologic concept.

The progress of psychosomatic medicine was the result of three main factors: the ever growing pressure of the clinical problems posed by the increase of neuroses and chronic diseases; the study by Cannon and James of the somatic expression of the emotions; and the advances in the psychology of behavior.

All this made possible the scientific study of emotion and the restoration of its true meaning, which had faded just as the image on a coin finally fades from constant use.

An avalanche of contributions in the field of psychosomatic medicine finally chiseled out of the mountain of psychiatry the new profile of psychobiology. We need only remember the work of Groddeck (1908), considered by some as the father of psychosomatic medicine; the psychogenesis and psychotherapy of organic symptoms formulated by Schwarz in Vienna; the work of Ludwig Krehl in medical anthropology; the studies of Siebeck and von Weizsäcker in Heidelberg creating a biographic medicine—a *graphos* of the human *bios*—and the work of Karl Jaspers differentiating diseases predominantly *biologic* from diseases essentially *biographic*.

After that, psychosomatic medicine flourished in this country, where it represents an important current of contemporary American medical thought—the triumph of the philosophy of psychobiologic unity over Cartesian dichotomy.

HALLUCINOGENIC DRUGS

The newest and most revolutionary method of research and therapy in psychobiology is the use of hallucinogenic compounds.

The use of drugs in psychiatry dates back almost to the dawn of history. Greek physicians used hellebore to treat "lunatics," and the literature of medieval times is prodigal in examples of brews and concoctions that could induce insanity and in some cases "cure" it.

Drugs were used in psychiatry always with the idea of soothing, calming, or drowsing the mental patient by affecting his conscious mind. Ninety-nine years ago bromides were discovered and later, barbital. In 1934 seismotherapy was introduced with the shock therapies.

None of these agents, however, served to reach the three great goals of psychiatric management already mentioned: to consider the mental patient as a *patient*, to reduce his agitation, and to improve communication between him and the psychiatrist.

In 1943, there occurred one of those happy accidents that have often contributed to the progress of science. Hoffman of Basel, Switzerland, accidentally induced in himself a pocket-size psychosis by swallowing some lysergic acid diethylamide. This was followed by a splendid study by Stoll, demonstrating that this and similar substances afforded psychiatry chemical keys that would open doors and project some light into the dark world of psychoses.

These hallucinogenic drugs, called in the past "phantastica" by the Germans, were used

for many centuries by primitive people to provoke religious ecstasies (among them was the cohoba used by the American Indians in the times of the Spanish Conquistadores). They were also amply used in medieval brews. In the second half of the nineteenth century some of these drugs, for instance, hashish, were consumed by the so-called decadent French poets to stimulate mental imagery, such as embellishes the poems of Rimbaud and Baudelaire.

A new way of communicating with the mental patient was through the use of agents like mescaline, bufotenin, and others which act as chemical keys that open and close at will some of the locked doors that lead to the mental imagery and perhaps to the pathogenetic mechanisms of mental disease. The replacement of shock therapies, in some cases by a more humane psychochemotherapy, has started a revolution in the management of the mental patient and in psychiatric research.

RESERPINE AND CHLORPROMAZINE

While this work was in progress, Dr. Rustom Jal Vakil, of King Edward Hospital in Bombay, India, had been, since 1940, using a centuries-old Indian root called *Rauwolfia serpentina*, an *ajurvedic* medication of mythologic lineage. Vakil treated with *Rauwolfia*—today called reserpine—thousands of patients suffering from hypertension and published the results in 1949 in the *British Heart Journal*. This paper eventually reached Dr. Robert A. Wilkin, of the Massachusetts Memorial Hospital, who obtained and used samples of *Rauwolfia*, describing in 1952 their sedative effect at a meeting of the New England Cardiovascular Society.

In 1953 Dr. Raymond Harris, of the Albany Medical College, confirmed the tranquilizing effect of *Rauwolfia* on mental patients, and in 1954 he was followed by Dr. Nathan S. Kline, Director of Research at Rockland State Hospital in New York. The mythical *ajurvedic* drug of the Orient, whose tranquilizing effect was known several centuries ago in India, was at long last confirmed by the modern science of the Occident.

Meantime, in Paris an investigation of antihistamines had been started with the purpose of finding one that would not produce excessive drowsiness. This research eventually led to the discovery of 4560 R.P. (chlorpromazine) at the Rhône-Poulenc Laboratories. With this compound, Madame Courvoisier in 1951 "cured" the anxiety experimentally produced in rats, and Laborit, in 1952, the anxiety suffered by human patients including pregnant women. In the same year, Jean Delay and Pierre Deniker used it successfully in mental patients; in Canada, Lehmann, and, in the United States, Winkelman and others introduced it in different clinical fields of psychiatry.

THE CONCEPT OF THE ATARAXICS

Thus it became possible to use a group of drugs that since then has increased to more than 25 tranquilizing agents now under investigation. Some are endowed with the property of interrupting experimentally induced psychoses and tranquilizing mental patients.

To these drugs Dr. Howard Fabing of Cincinnati, supporting a suggestion from the professor of classical languages Alister Cameron, gave the name "ataraxics." Under this

name is included a variety of drugs pertaining to the groups of indoles, piperidines, and phenothiazines. Their effect is said to produce ataraxia, that is to say, they leave the patient *ataraktos*, "without confusion," "with peace of mind," this being a beloved word of the classical epicurean philosophers because it represented their most cherished philosophic goal.

A PAUSE BEFORE THE MYSTERY

We still do not know the mode of action of the ataraxics, the most powerful weapon of psychobiology. Maybe they act on the hypothalamus—that tiny islet of nervous tissue, refuge of whatever instincts remain from our hairy prehistoric ancestor who lurked in the dark primeval forests. Maybe the ataraxics act also on the neurovegetative system. They especially seem to act upon the reticular formation of the cerebral cortex, the archaic paleocortical-hypothalamic-mesencephalic system that regulates the primitive urges of hunger and sex and the interrelationship with other living beings; they also act upon the mesocortical-reticular-endothalamic system, which adapts the human being to the temporal-spatial circumstances of the outer world and contains a condensed representation of the peripherical structures.

It is also possible that the ataraxics, to paraphrase Selye's concept, in their action "imitate and if necessary correct and complement the body's own auto-pharmacologic efforts to combat the stress factor in disease."

The possibilities that these compounds offer for research in psychochemotherapy are unlimited. For example, the mental imagery observed in patients treated with these drugs coincides with the imagery in the literature produced by great poets and mystics, such as Baudelaire, Coleridge, Poe, De Quincey, St. Teresa, and St. John of the Cross. Conversely, the artistic productions of persons treated with the hallucinogenic drugs have a striking resemblance to the early works of Picasso, Braque, and some of the surrealist painters. We welcome in this direction the work in progress of Werner Wolff, who is trying to determine the relationship between drugs and poetry.

Considering the similarity between the mental imagery of geniuses and that of persons under the effects of these drugs, one is bound to think that perhaps the organic production of certain substances—a gigantic chemical mistake of the human body—may in some cases originate schizophrenia. In milder instances, when these substances are produced under the stimulation of fast, self-hypnosis, or toxic drugs, they may determine literary and artistic imagery. Perhaps some day we may discover part of the secret of genius through the study of body chemistry.

The horizon is unlimited and the bright dawn seems to herald a radiant day.

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Stress and Psychobiology*

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It is with much pleasure that I accepted the Editor's invitation to present a synopsis of our work on the occasion of this Clinical Round Table. Our investigations on the relationship between stress and the nervous system are concerned mainly with the endocrine aspects of this topic. I shall therefore restrict my presentation to stress and the endocrines as a means of integrating biologic and psychologic reactions. Before doing this, however, I should like to mention a few of the most important key references to the purely neurophysiologic aspects of this problem, i.e., Army Medical Service Graduate School, 1953;[1] Basowitz et al., 1954;[2] Cannon, 1939;[3] Galdston, 1954;[4] Grinker and Spiegel, 1945;[5] Hess, 1954;[6] and Wolff, 1953.[13]

THE CONCEPT OF STRESS

As early as 24 centuries ago, Hippocrates taught his disciples that disease is not only suffering (*pathos*) but also toil (*pónos*), i.e., the fight of the body to restore itself toward normalcy. About a century ago, Claude Bernard pointed out that one of the most characteristic features of all living beings is their ability to maintain the constancy of their internal milieu, that steady state that Walter Cannon named "homeostasis." At that time it was felt that any deviation from the steady state, or at least the effort of restoring a homeostatic equilibrium, was possibly stress. If so defined, the concept of stress would include all physiologic deviations from the normal resting state, and, yet, in conversational English, it implied a particularly strenuous and usually damaging condition. Furthermore, the term was used by some authors as virtually synonymous with nervous stress and strain, while others employed it to denote the consequences of any noxious agent. Additional confusion was created by the indiscriminate use of the same term for the agent (trauma, emotions, infections, and cold) and the effect (morphologic and functional changes in the body) of exposure. This vagueness in the formulation of the subject is probably responsible for the fact that, although the importance of stress in medicine has always been recognized, it has not been possible to submit it to systematic investigations until quite recently.

AN OPERATIONAL DEFINITION OF STRESS

It was the discovery that stress always manifests itself in the form of a definite, stereotyped syndrome that helped us to arrive at what philosophers call an "operational definition" of this condition. It became evident that stress, no matter how produced, elicits certain changes, quite typical and specific, in the body, such as adrenocortical stimulation, involu-

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tion of the lymphatic organs, and gastrointestinal disturbances. Those alterations served as objectively measurable indicators of stress and led to the following definition: Stress is the state manifested by a specific syndrome which consists of all the nonspecifically induced changes within a biologic system. In this sense, stress has its own characteristic form but no particular cause.

This is an essentially operational definition in that it tells us what must be done to produce and recognize stress. A state can be recognized only by its manifestations: for instance, the state of stress by the manifestations of the stress-syndrome or "general adaptation syndrome." Therefore, we must observe a great many living beings exposed to a variety of agents before we can see the shape of stress as such. Those changes that are specifically induced by only one or the other agent must first be rejected; if we then take what is left, that which is nonspecifically induced by many agents, we have unveiled the picture of stress itself.

I may say that it was tempting at first to define stress merely as "the rate of wear and tear" within the body, because this is the immediate nonspecific result of both function and damage. Reactions that tend to diminish or repair wear and tear (e.g., corticoid secretion) are not strictly stress but rather defenses against stress. In practice it is impossible, however, always to differentiate sharply between a change that represents repair and one that is merely damage. Therefore, this formulation, though more concise and theoretically more satisfying, could not have acted as a basis for a truly operational definition such as was needed to give the concept of stress a solid, objective foundation.

The enormous literature on stress, the general adaptation syndrome, and the so-called adaptive hormones (now comprising more than 25,000 references to original articles and books) has been reviewed in detail elsewhere.[7, 8, 9, 10, 11, 12] In all these reviews special emphasis was placed upon the relationship between stress and neuropsychiatric problems. Hence it will not be necessary to complicate this review by a confusingly voluminous bibliography, and I shall limit myself here to a brief discussion of certain experimental observations that, to my mind, may have interesting applications in psychobiology.

MUSCULAR PARALYSIS

In dogs given prolonged treatment with desoxycorticosterone acetate (DOCA), R. Loeb and his associates, in New York, have observed a syndrome reminiscent of periodic muscular paralysis. We have obtained quite similar changes in a primate, the rhesus monkey, and noted that attacks of paralysis can be produced in DOCA-treated animals at will, any time, by giving them large amounts of sodium chloride. In the production of these paralytic spells there appears to be some synergism between mineralocorticoids and sodium. Conversely, intravenous infusion of a potassium chloride solution can restore the DOCA-overdosed dog or monkey to normalcy within a few minutes.

It is especially noteworthy in this connection that Dr. J. W. Conn observed quite comparable manifestations of muscular paralysis in a woman in whom an adrenocortical tumor produced an excess of aldosterone (a mineralocorticoid, chemically and functionally closely

related to desoxycorticosterone). Interestingly, in Dr. Conn's patient, as well as in several others observed since, the hyperaldosteronism that led to these motor disturbances did not produce edema; conversely, in nephrosis, when urinary aldosterone elimination becomes excessive, there is much edema but no muscular paralysis. Future research will have to show why an excess of such a mineralocorticoid can produce more or less selectively one or the other type of manifestation in different patients. Animal experiments have already shown that hormones, such as DOCA, can act rather specifically on one or the other target, depending upon what we call "conditioning factors." DOCA, for instance, produces nephrosclerosis, hypertension, and periarteritis nodosa in rats, or muscular paralysis in dogs and monkeys, much more easily when the sodium intake is high, but the anesthetic effect of the same hormone is not thus enhanced by the salt intake.

MORPHOLOGIC CHANGES IN THE BRAIN

In rats heavily overdosed with desoxycorticosterone (especially if they are sensitized by a high sodium chloride intake and unilateral nephrectomy) there develops an encephalopathy with periarteritis nodosa of the cerebral vessels, marked edema, and often multiple massive hemorrhages in the brain. These lesions are accompanied by convulsions or paralytic changes in the skeletal musculature and by an extreme irritability of the animals. It is possible to prevent such changes by the administration of acidifying salts, for instance, ammonium chloride or calcium chloride.

The question arises as to whether cerebral changes, such as are seen in clinical periarteritis nodosa and in hypertensive disease, are related to the excessive production of mineralocorticoids or an excessive conditioning for their actions. In any event, this experimental encephalopathy now serves as a useful test object for the screening of drugs that may have clinical applications in those diseases of man simulated by DOCA overdosage.

THE INFLAMMATORY DISEASES

It is now a generally accepted fact that certain adaptive hormones produced during stress (ACTH, cortisol) have definite anti-inflammatory actions; it is less certain but highly probable that, under special circumstances, stress and the so-called prophlogistic hormones (e.g., somatotropic hormone, DOCA, aldosterone) actually stimulate inflammation and the development of the so-called collagen diseases in man.

Our attention was called to the relationship between inflammation and the adrenal in the course of experiments on the "anaphylactoid inflammation." It had been noted in 1937 that the intraperitoneal or intravenous administration of egg white produced a peculiar hypersensitivity reaction in the rat, characterized by a pronounced inflammatory edema in the snout, the paws, and the ears. It was immediately obvious that the adrenal played an important role in this response, because, after adrenalectomy, stress failed to prevent this reaction to egg white. From this we concluded that stress presumably inhibited inflammation through the excessive production of ACTH and antiphlogistic corticoids. At

the time of our first experiments, purified preparations of ACTH or synthetic anti-inflammatory corticoids were not yet available, but more recently we have been able to show that these hormones also inhibit this type of inflammatory hypersensitivity reaction, just as exposure to stress does.

All of these facts have been confirmed with a variety of other tests that we have developed for the quantitative assessment of inflammation caused by ordinary chemical irritants (e.g., topical irritation arthritis produced with formaldehyde or "granuloma pouch" produced with croton oil). In all of these instances, inflammatory changes due to tissue irritation have been inhibited, not only by stress due to somatic causes (trauma, burns) but also by such neuromuscular stress as is induced by forced immobilization. Still, stress, no matter how induced, did not exert this inhibitory effect after removal of the adrenals.

The converse effect, namely, the stimulation of inflammation by stress and by adaptive hormones, has also been demonstrated in animal experiments, but it is not yet clear to what extent these findings are applicable to the problems of clinical medicine. Prolonged overdosage with DOCA (especially after sensitization by excessive salt intake) produces periarteritis nodosa and myocarditis; it also sensitizes for the production of various types of experimental arthritis in the rat. Furthermore, under suitable experimental conditions, the antiphlogistic effect of cortisone or cortisol can be inhibited by DOCA or aldosterone in animals. It is clear, therefore, that, at least in certain mammals, the "inflammatory potential" (the ability of tissues to undergo inflammation) depends largely upon the balance of proinflammatory and anti-inflammatory hormones. It is highly probable that, in man, the hormonal regulation of inflammation obeys essentially the same rules, but the clinical effectiveness of the prophlogistic principles has not yet been explored as completely as that of the inversely acting hormones.

The importance of the balance between proinflammatory and anti-inflammatory hormones for the regulation of inflammation has several interesting implications in the field of psychosomatic medicine. For example, it has long been known that certain infectious diseases, for instance, tuberculosis, may be greatly aggravated by exposure to virtually any kind of severe stressor. The rest cures for tuberculosis are based upon the empirically established fact that protection from stress is an important aspect in the healing of tuberculous lesions. Animal experiments, for instance, have shown that in the rat (a species normally resistant to tuberculosis) overdosage with cortisone can induce great sensitivity to tubercle bacilli, while the antiphlogistic somatotropic hormone restores resistance to normal, despite continued cortisone treatment. Even normally saprophytic micro-organisms tend to spread and become highly pathogenic in rats overdosed with ACTH or cortisone; here again, the somatotropic hormone exerts a protective effect. It is probable that, to a large extent at least, the antiphlogistic hormones favor the spreading of infection because they remove the inflammatory barricades around the foci of micro-organisms, while the proinflammatory hormones act inversely by stimulating granuloma formation and the encapsulation of potentially pathogenic germs. Numerous clinical observations have shown that heavy and prolonged overdosage with antiphlogistic hormones in man can also induce the spreading of an originally innocuous and well-delimited tuberculous process.

One of the first observations concerning the alarm reaction (the first stage of the general adaptation syndrome) was that stress produces gastric and duodenal ulcers in animals. It has since been shown, both in experimental animals and in man, that overdosage with antiphlogistic hormones may likewise cause the development and even the perforation of peptic ulcers. This may explain the empirically established relationship between stress (particularly neurogenic stress) and peptic ulcer formation.

In experiments designed to elucidate the mechanism of this phenomenon, we were able to show that peptic gastric juice, introduced into an experimentally prepared granuloma pouch, does not digest the wall of this sac, because the inflammatory tissue is extraordinarily resistant to peptic digestion. On the other hand, exposure to the stress of forced immobilization causes such a weakening of the granulomatous barricade that it is readily attacked by peptic juice. In the absence of the adrenals, exposure to similar stress does not thus affect the resistance of granulomatous tissue. It is highly probable, therefore, that the antiphlogistic effect of the adaptive hormones produced during stress plays an important part in the perforation of peptic ulcers; it diminishes the resistance of the granuloma tissue that normally covers the crater of gastroduodenal ulcers.

The important clinical observations of Dr. Seymour Gray have shown that the secretion of peptic enzymes is enhanced during the alarm reaction by stress and also during treatment with antiphlogistic hormones (e.g., ACTH and cortisone). Consequently, during stress, the perforation of peptic ulcers is presumably facilitated through a dual mechanism: the resistance of the protective granuloma wall is diminished, and the secretion of the aggressive enzymes is augmented.

SUMMARY

After a brief enumeration of key references to the literature on stress in psychobiology, the following specific problems are discussed on the basis of personal experiments: (1) an "operational definition" of stress; (2) muscular paralysis; (3) morphologic changes in the brain; and (4) the inflammatory diseases.

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Dr. Co Tui Invited by President of Philippines to Conduct Medical Survey

Co Tui, M.D., Associate Research Scientist at Creedmoor Institute for Psychobiologic Studies in Queens Village, New York, has been honored with an invitation from President Magsaysay of the Philippine Islands to conduct a broad survey on all scientific needs and development in that country. He will spend six weeks there on this project and then tour Europe before returning to Creedmoor.

Dr. Co Tui has been engaged in medical research since 1929. From 1932 through 1949 he was Associate Professor of Experimental Surgery at New York University College of Medicine. In 1937 he founded the American Bureau for Medical Aid to China and was decorated by its republican government; he headed a special medical mission to China in 1946. He joined the staff of Creedmoor in 1949 as Director of Biologic Research.

Dr. Co Tui is a member of the New York Academy of Medicine and of the Society for Experimental Biology and Medicine as well as of other professional organizations. He is also Honorary President of the International Anesthesia Research Society.

He has made numerous contributions to medical journals, including the Journal of Clinical and Experimental Psychopathology.

At present, he is interested in adrenocortical function and the ataractic drugs. Psychiatric patients from Creedmoor and from other hospitals are the subjects of his studies.

Experimental Pharmacodynamics and Psychobiology*

A. Hoffer, M.D., Ph.D.

DIRECTOR OF PSYCHIATRIC RESEARCH, PSYCHIATRIC SERVICES BRANCH, DEPARTMENT OF PUBLIC HEALTH, AND ASSISTANT PROFESSOR OF PSYCHIATRY, COLLEGE OF MEDICINE, UNIVERSITY OF SASKATCHEWAN, SASKATOON, SASKATCHEWAN, CANADA

Goodman and Gilman's[1] description of factors that modify drug action include dosage, tolerance, idiosyncrasy and hypersensitivity, influence of the pathologic state (in the physical sense) and cumulative action. The subject of my discussion is the omission of another factor, that is, the psychologic state, also omitted by Drill.[2] These omissions are surely most curious. The whole field of psychiatric theory of drug action obviously is ignored by classical pharmacology. Recently, however, some eminent pharmacologists have begun to correct this error.

From the earliest evidence of history, physicians have treated patients with drugs and ascribed success or failure to the drugs. Although a few were aware of the importance of the expectations of the patient, it is only recently that this phenomenon has been described and recognized as a fruitful field of study.

Pharmacology, the most objective study of drug activity, leans most heavily upon the action of drugs on isolated animal tissue, less reliably on the intact animal. The psychologic expectations of the animal have been considered relatively unimportant, although more recent work indicates that this can not be ignored. Having seen the action of drugs on animals, it is assumed that similar effects might occur in man, and often this is true. Unusual reactions are, however, forgotten or labeled as idiosyncrasies. This is the status of pharmacology today, if textbooks of pharmacology are representative, except for a few pharmacologists and workers in two fields, the anesthetists and psychiatrists. The interest of the anesthetist is historically correct since the first anesthetic suggestion was made in 1799 by Sir H. Davies, a chemist, regarding the use of nitrous oxide for anesthesia.

Following the pioneer work of Wolf and others, we have become aware of the psychologic or placebo factor that no longer can be ignored. "Experimental Pharmacodynamics and Psychobiology" is an awkward title for a relatively new field of study. No single word as yet proposed has appeared suitable to me. My colleague, Dr. H. Osmond, has proposed the word "psychedelic," meaning "mind manifesting," for the class of drugs which, when taken internally, make manifest many aspects of the mind for experimental study. "Psychedology, or a Study of Psychedelic Drugs," would be a better term than "Pharmacodynamics" since our field of study refers more to the effect of drugs on mind processes than on physiologic processes, which physiologists and pharmacologists deal with. The whole man is an ideal abstraction in research; he must be broken into fragments amenable to study.

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*Presented at the Round Table Dinner Meeting of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY, American Psychiatric Association, Chicago, Ill., May, 1956.

When any drug is administered, there are three factors, or areas of reactivity: (1) the psychologic, which depends upon the integration of the personality and experience of the individual; (2) the effect of the situational anxiety (placebo effect) upon the first factor; and (3) the effect of the administered drug on the first and second factors. It is possible to study the first factor in great detail with advanced psychologic and analytic techniques, but it is never possible to exclude it. The second factor may be similarly studied and by proper experimental design may be reduced to manageable proportions. Having done both of these, it becomes possible to study the third factor, which would most closely represent the drug effect upon animals.

These methods are applicable for the study of well-known drugs such as lysergic acid diethylamide (LSD), as has been done by Abrahamson with a double-blind procedure. However, this type of study is exceptional and so infrequent that today, in my opinion at least, there is very great doubt as to whether we really know the effect of LSD or mescaline on humans. I believe that we do know what effects these drugs have when the first two factors are considered, but we have not isolated the third factor; perhaps this is impossible.

Last year at the American Psychiatric Association meeting in Atlantic City, N. J., it was reported that the daily administration of LSD resulted in a decreased response. After five days of rest, a strong response was again obtained. It was assumed that previously administered dosages of LSD acted as an antagonist. This was summed up by Abrahamson who stated that the best blocking agent for LSD is LSD. This probably is correct, but only in so far as it is the result of a gradual decrease of anxiety due to familiarity with the situation so that, at the end of five days, one is combining only the first and second factors. whereas on the first day one would have a combination of all three factors. In other words, the apparent response to LSD as a blocking agent may be in effect merely a decrease in experimental anxiety. We have carried on some research with 10 to 15 μg. of LSD given at weekly intervals and have noted that no one in the group was able to differentiate this quantity from the placebo but that in a few instances a combination of anxiety plus this quantity of LSD produced a striking reaction that was later much more intense. Agnew and Hoffer reported that nicotinic acid antagonized some of the LSD changes. It appears possible here also that nicotinic acid may have decreased the anxiety due to the knowledge of the individual that it might be an antagonist. This applies also to the study of other antagonists, for example, α-(4-piperidyl)benzhydrol hydrochloride (Frenquel), chlorpromazine (Largactil), and reserpine.

It is therefore essential that drug experiments be so performed that one can rule out, where possible, the first factor. Until this is done, we can only say that we know the effect of drugs when all three factors are present. We would like to know the effect of drugs with omission of the second factor.

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Psychobiologic Advances and the Management of Hospitalized Patients*

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I might possibly summarize in another phraseology what has already been said, what I call my pendulum theory of psychiatric history.

Actually, you know, the pendulum *has* swung in psychiatric treatment. I am concerned primarily with the point at which psychiatry began. I haven't been able to keep up with where it has gone.

The history of the treatment of mental illness and of some of the theories that lay back of it has swung from one extreme to the other through the years. In the early days of Benjamin Rush, the theory of causation was entirely somatic. The prevailing view reiterated and extended by Rush was that the causation of mental illness was strictly physiologic and organic. For this reason, the psychobiologic treatments of his time consisted in bleeding, purging, and, if I may use a brief but effective word, "puking." Depletion in general was the way to treat a condition that was due to overdetermination of blood to the brain. In Europe, thanks to the motivation that was given initially by Pinel in France, Chiarugi in Italy, and Tuke in England, the trend, which later also became prevalent in America, had a humanitarian basis and became primarily psychological. The impingement of the environment on the patient, kindness and pleasant surroundings was what Pinel referred to as moral treatment or, as we would say today, psychotherapy of the milieu variety.

Drugs have been used off and on during the ages. There is nothing new about the use of drugs. There were times when they were used very freely, and other times when the fashion swung in the other direction.

More recently we have seen the rise of specialized forms of psychotherapy. Among these, group psychotherapy is one of the few American contributions to therapy, the only other distinctively American contribution noted by me being the sodium-amytal interview. These forms of psychotherapy, notably the analytic or modified analytic variety, have gained ascendancy with, at times I fear, a somewhat corresponding diminution in interest in the physical organism carrying the particular psychology in question. As a result it seems that some of our colleagues have been inclined to look upon the patient as presenting a disembodied mind and have paid relatively little attention to some of the physical factors within or without the patient.

More recently we have seen again the rise of some of the physical methods, namely,

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insulin shock, electroshock, metrazol shock, and some of the even more drastic therapies that are perhaps hardly deserving of the name therapy, particularly lobotomy.

We now have a different approach, a recrudescence in another form, of one of the most primitive types of treatment, namely, drugs. At least they are useful as adjuvants, if nothing more. We now have the great advantage of two ataraxic drugs at least—and very likely will have many more shortly—namely, chlorpromazine and reserpine, which have the merit of calming the patient without seriously impairing consciousness. The patient remains alert and remains in contact with what is going on about him but is not driven by anxieties and may be physically considerably calmed. Overactivity is reduced.

I have had an opportunity to see what these ataraxics can do in a hospital. We have about 7000 patients at St. Elizabeths and some have been rather disturbed at times. For about two years we have been using these two ataraxics with considerable enthusiasm and certainly with very striking results. Therefore, I thought I might summarize briefly some of the results and how the effects spread through the atmosphere of the hospital into the atmosphere of the community.

Of course, first of all, you know what the ataraxics do to the patient. They do cut down activity. They make the patient more composed and he is much less worried about himself. He can discuss his hallucinations and delusions without stirring up previously manifested anxieties. Thus he becomes more communicative and more accessible to the approaches of the physician, to other people in his surroundings, and responds to various environmental events.

I fear that some legislators are going to get the idea that all you have to do to regain your sanity is to buy a few bottles of the pills and take them. As a result, they are likely to think that we are going to have much less need of people to look after the patients. As a matter of fact, I think we need more. The patients need more attention while in the hospital; they are much more demanding of the attentions of those about them. A few bottles of these ataraxics cannot be substituted for the services of nurses and attendants and physicians and psychologists. There is, however, a very fair chance that we are going to be able to send our patients back to the community sooner. We are going to cut down the time of hospitalization and increase the number of patients discharged.

Incidentally, it looks as though a good many physicians in the community are prescribing ataraxics. I cannot otherwise explain the fact that for the last six months there has been a more than seasonal drop in the admissions to St. Elizabeths. We have been at the same time increasing the number of patients on visit and on discharge, so that actually the hospital population is falling. I submit that this is all to the good.

Perhaps there are two difficulties that the people in the community are likely to encounter, especially the physicians. One is that the physicians may be timorous about giving the amounts of ataraxics really needed to produce an effect. I think some physicians may give too small an amount with the result that they say in disappointment, "Why these drugs are no good." The other difficulty is that some people do not realize the possible complications. These complications reflect nothing against ataraxics. I do not know of a therapeutic instrument of any sort that is of value that cannot, in the wrong hands, ap-

plied at the wrong time or in the wrong amount, be detrimental to the patient. If you have something that is 100 per cent safe and results in no complications, you can be sure that is is not worth very much.

In the hospital there are fewer assaults and fewer altercations; there is less destruction and less need of seclusion. The atmosphere of the ward is a comfortable, pleasant one with a good deal of interest manifested in what is going on in the way of activities, recreation and so on.

This atmosphere has an effect on the nurses and doctors, in that it makes them more interested. It makes them feel a bit more optimistic when they see a patient who has been a serious problem for a long time responding to ataraxics, his whole attitude changing. It changes theirs, too. The community, then, benefits by these changes in attitudes.

Undoubtedly some false hopes are raised. We have no panacea yet, but certainly the community is beginning to realize we have an additional weapon now in our armamentarium that can be helpful in treating the patients and in restoring them to normal at least temporarily, probably permanently in a great many cases. Apparently the administration of ataraxics can be carried on for a fairly long time.

In the long run we are going to have a by-product. Once the legislators get over the notion that they can avoid adding personnel by buying pills, they will think of institutions again. They are gradually coming to this line of thinking anyway. A tremendous impetus has been given to hospitals, not as asylums but as hospitals as treatment centers and not as receptacles where the patient goes to spend the rest of his days.

Do not forget that there are many, many peculiar notions in the minds of the people in the community about mental hospitals, but certainly these attitudes are changing. Ataraxics are having a good deal to do in furthering and promoting that change.

We are swinging, and I think the pendulum is going to continue swinging. It is always well to remember that the pendulum never swings half way in America; it always swings across a very wide arc, and we do not know just when it will start to swing back.

I have an idea that perhaps it will not swing back quite so far as it may have in the past. We may not have a substitute here for some of the other forms of therapy, but I am sure that these two ataraxics particularly have changed many features of hospital care for the better.

Change in Title of International Record of Medicine

Beginning with the January, 1957, issue, the title of the journal, International Record of Medicine & General Practice Clinics, will be changed to INTERNATIONAL RECORD OF MEDICINE. The official abbreviation of this title for bibliographic purposes will be: Internat. Rec. Med.

Recent Advances in "Pharmaco-psychiatry"*

Pierre Deniker, M.D.

PARIS, FRANCE

The term "pharmaco-psychiatry" is a neologism that has been criticized but that covers the most active research being done at the present time, namely experimental psychopathology conducted with psychopathogenic drugs and new psychiatric chemotherapies.

The relationship between these two branches of modern psychiatry lies in the fact that certain experimental intoxications have been the starting point of some therapeutic experiments and, further, that new drugs for psychiatric treatment have appeared to be effective as antagonists of experimental intoxication.

EXPERIMENTAL PSYCHOPATHOLOGY WITH CHEMICAL AGENTS

Since the time when Moreau de Tours attempted to find the secret of insanity in the intoxication acquired from the use of *Cannabis indica*, psychiatrists have been interested in explaining the mechanism of hallucinations and delusions, which are undoubtedly the most mysterious aspects of mental disease, and in clarifying the complex problem of the genesis of schizophrenia.

After hashish, mescaline, cocaine, and other compounds were used experimentally with attention most recently directed toward compounds such as amphetamine, LSD, derivatives of epinephrine, and serotonin. Generally, experimenters started with explorations on animals and on themselves. Experiments on mental patients are more recent and still limited in number.

This survey is concerned with the action of two drugs that have some chemical relationship, methylamphetamine and mescaline, which we have studied at the Clinique des Maladies Mentales de la Faculte de Paris.

Amphetamines, especially methylamphetamine are well-known psychotonics that are capable of increasing verbal exteriorisation. In the field of psychoses, J. Delay[1] has used methylamphetamine for diagnosis and nosography. In psychoses that alter the thymic state, that is, in manic-depressive states, which is a hyperthymic state, and in schizophrenia, which is an athymic state, methylamphetamine often tends to aggravate the symptoms and even bring them to light. The manic becomes more excited and is more logorrheic. The melancholic patient may become more inhibited, or, on the contrary, his anxiety may become manifest. In some cases of incipient schizophrenia the drug may bring about an early manifestation of symptoms, especially such signs as those of the catatonic type that may help establish the diagnosis.

With Delay and Pichot, in 1950 we reported[2] some therapeutic and paradoxical effects. Strong doses of methylamphetamine administered to maniac patients could transform their

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condition temporarily into true melancholia and in some patients bring about a cure of the excitation states—all with an analeptic drug. This observation may be somewhat similar to recent therapeutic findings observed after administration of mescaline.

Mescaline, since Hefter, has tempted not only psychiatrists but writers and poets also. Its use for diagnostic and therapeutic purposes is more recent.

The studies we are now conducting in France[3–5] show that, between sane subjects, such as voluntary experimenters, and psychotic patients, important differences can be noted in their reaction to mescaline. Whereas in sane subjects the drug seems to produce qualitative psychic modifications such as the creation of psychosensorial symptoms, in psychotic subjects the drug usually brings about only quantitative modifications such as an increase or uncovering of classic signs of the disease. The appearance of hallucinations is relatively rare (about one fifth of the cases) and patients who previously had hallucinations are not greatly improved. Inexpressible anxiety, induced by injection of 1 cg./Kg. of mescaline, has been used by American investigators for psychoanalytic objectives and therapy. We have, however, attempted to study the humerovegetative modifications that follow administration of such doses of mescaline.

In 25 male patients changes were observed that were fairly regular. After early mydriasis, congestion of the face, cyanosis of the extremities, perspiration, and nausea, the pulse rate increased about 28 beats/minute in a four or five hour period. Blood pressure increased by two figures from 2 to 5 cm. of mercury up to the fourth hour. The temperature at first decreased, then increased to 38 C. In the fourth hour, the respiration became hyperpneic and the oculocardiac reflex became indifferent.

Blood sugar increased on an average of 35 per cent, with a maximum increase occurring 30 to 60 minutes after injection, whereas blood potassium was reduced by 16 per cent. During the same period, sodium, chlorine, and protein remained unmodified. Leukocytes increased and were approximately double in number between the second and the fourth hour. The eosinophil count (Thorn test) showed an average decrease of 95 per cent, the maximum decrease occurring at the fourth hour. Urinary excretion by 17-ketosteroids the day following administration show an average increase of 42 per cent in 10 of 17 patients, and in 6 patients a decrease of 24 per cent was noted. The electroencephalogram showed a lowering of the curves.

All these biologic reactions closely resemble those of the alarm state. However, it is difficult to ascertain whether these reactions are due to the direct action of the drug or to the extreme anxiety the drug usually causes. Thus, the stress may be psychic as well as biologic.

The use of chlorpromazine as an antagonist of the state produced by mescaline gave us as it did Denber and Merlis,[6] spectacular effects, such as suppression of the mescaline-induced state. However, at this time, we have noted few significant therapeutic results that were unexpected, since treatment constitutes true mescaline shock.

NEW PSYCHIATRIC CHEMOTHERAPY

In 1952 chlorpromazine reopened the field of chemotherapy. Two years later, the alka-

loids of Rauwolfia serpentina, although chemically different, were shown capable of producing similar effects. Since that time experimenters have been beseeched to try new drugs presented as "potentiators" or ataractic agents. In fact, psychiatric chemotherapy did not start with chlorpromazine, and it is probable that today opium, jusquiame, paraldehydes, or barbiturates would be qualified as ataractic drugs.

The time has come, therefore, to establish some definite criteria for the new drugs that Delay called *neuroleptics*, of which chlorpromazine and reserpine are the primary ones, although chemically different. In the establishment of such criteria neither a chemical group nor pharmacologic effects such as potentiation or anesthetic effect can be used. We have proposed therefore[7] the use of psychophysiologic criteria employed in the clinic as well as in the laboratory.

1. The essential feature of neuroleptics is their sedative, and sometimes hypnotic action; they do not, however, have a narcotic effect, that is, they do not produce irreversible sleep. In man, they produce a state of *indifference;* in animals, high doses may be given without creating a deep sleep, and it is possible for the animal to be aroused with a light stimulus. The catatonic action in some animals is not specific; on the contrary, the drugs, in general, suppress the conditioned reflexes of animals.

2. Their effect on excitation, restlessness, and aggressiveness, whether pathologic or not, is also of primary importance. This has been demonstrated on naturally aggressive animals. The drugs can, even in low doses, quiet the sham rage of animals having undergone decortication. In the film,* which we will present, the action on experimental restlessness of whirling mice treated with imino dipropionitrile is shown. Such effects are similar to those obtained in agitated patients in psychiatric hospitals with the introduction of the new drugs.

3. Some psychiatric syndromes appear to be especially influenced by these drugs, and this is a true pharmacologic test of such drugs. The action on the manic type of agitation states on mental confusion, and on anxiety and insomnia have been underlined repeatedly in the

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* It has been found that the injection of $\beta\beta'$ imino dipropionitrile (Buc, S.: Organic Synthesis, vol. 27, p. 3) produces in mice a persistent hyperkinesis that is very useful pharmacologically in testing sedatives (Delay, J.; Pichot, P.; Thuillier, J., and Marquiset, J. P.: Compt. rend. Soc. de biol. 146:533, 1952; Thuillier, J.; Burger, A., and Mouille, P.: Compt. rend. Soc. de biol. 147:1052, 1953; Thuillier, J., and Burger, A.: Experientia 10:223, 1954).

To produce the syndrome, 1.50 Gm./Kg. of $\beta\beta'$ imino dipropionitrile were injected into mice weighing about 20 Gm. (subcutaneous or intraperitoneal injections are convenient). The injections are repeated every day or every two days. Four injections are sufficient. With use of the fourth injection, the animals show abnormal excitement, and after 10 days the syndrome is developed completely. Dancing mice live as long as normal mice; they eat and sleep normally, and their offspring are normal. Between periods of sleeping and eating, they spontaneously show a great hyperkinesis, turning about in both directions.

It has been observed that this psychomotor syndrome can be temporarily stopped by neuroleptic drugs such as chlorpromazine and reserpine (Delay, J.; Deniker, P., and Thuillier, J.: Compt. rend. Soc. de biol. To be published).

From "Dancing Induced in Mice by Administration of Imino Dipropionitrile: A Screening Test for New Psychiatric Drugs (Neuroleptics), 16 mm. 20 m. film, copyrighted by Clinique des Maladies Mentales, Paris, 1955.

last four years. More recently it has appeared that these drugs may have an action on chronic psychoses and schizophrenia. This observation was somewhat unexpected, since an ataractic drug is, in that case, capable of acting on the inhibitions of schizophrenic persons.

4. The simultaneous occurrence of neurovegetative modifications appears to be related to the action of such drugs; these changes, primarily related to blood pressure, pulse, and temperature, are brought about by the action of different mechanisms acted upon by chlorpromazine and reserpine. The extrapyramidal symptoms must also be noted.

5. The last criterion is the primary subcortical action (suspected from the psychic and vegetative effects). This action was demonstrated by two types of experiments. Dell showed by electroencephalography that suppression of sleep waves caused by pinching the sciatic nerve in the cat no longer occurred when the animal had been treated previously with chlorpromazine. Other experiments, in Philadelphia and Stockholm, conducted with radioactive tagged sulfur 35-chlorpromazine showed that the drug was stored in every part of the brain, but especially in the diencephalon.

Regarding reserpine, it has been noted that it displaces serotonin in the reticular formation, and the work now being done on this compound in relation to its action on mescaline and LSD 25 is well known.

CONCLUSION

Present and forthcoming progress in experimental psychopathology and psychiatric therapy is important indeed, but present methods are insufficient for full understanding and adequate treatment of mental disease. We should never forget our responsibility in providing proper diagnosis, psychotherapy, and rehabilitation for our patients. Only if these are done will the advances of neurophysiology and psychophysiology be effectively used.

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In Memoriam

H. Holland de Jong, M. D.

The death on Feb. 16, 1956, at the age of 61, of Dr. H. Holland de Jong, brought to an untimely end a life dedicated to science. (The last completed paper by Dr. de Jong is the opening article of the Symposium on Artificially Induced Psychoses on page 388.)

This famous psychiatrist, born in Sneecke, Holland, in 1895, studied in Amsterdam, first with Wertheim and Salomonson and then with Brouwer. His earliest investigations involved studying the control of palsy by means of bulbocapnine administration. Since my interest in the pathophysiology of catatonia and schizophrenia had proceeded along congenial lines, we decided in 1928 to work together. In the course of our collaboration we observed that bulbocapnine suspended psychomotor initiative in cats and produced phenomena resembling catalepsy, including negativism and neurovegetative disorders. These efforts eventually resulted in the production of experimental catatonia. Babinski himself felt it important to encourage us in our work.

H. Holland de Jong

From Paris we moved to Brouwer's laboratory in Amsterdam. There, thanks to the help of the Rockefeller Foundation, we were able to throw some light on the interrelations of sleep, catatonia, and epilepsy and on the phylogenetic implications of cerebral development. These efforts resulted in the joint publication of a monograph on *Experimental Catatonia with Bulbocapnine.*

Unfortunately, diverse opportunities for pursuing independent careers led to the discontinuance of our joint efforts. Dr. de Jong left Holland for the United States, and there, while working at Johns Hopkins and at Duke University, produced experimental catatonias through the use of varied chemical agents. Most importantly, he was able to demonstrate the hormonal (epinephrine) induction of experimental catatonia. Further investigations included the production of catatonic states surgically and through the administration of acetylcholine and mescaline. In the last years of his work, Dr. de Jong also became interested in the relation of the neurovegetative activities to the production of catatonia. His research involving the obliteration of the intestinal lumen and the ligating of biliary ducts undoubtedly led him to consider again the role that is played by hepatointestinal factors in catatonia, in particular, and, more generally, in schizophrenia. Dr. de Jong's tragic death abruptly ended a life dedicated to the intensive scientific investigation of the problems of psychiatric disease.—*Dr. H. Baruk, Paris, France.*

In Memoriam

Louis Cholden, M. D.

Those who attended this year's Chicago meeting of the American Psychiatric Association were shocked and saddened to learn that Dr. Louis Cholden had been killed in an automobile accident on his way to the airport to catch a plane for Chicago. As one of the nation's young and rising psychiatrists, Dr. Cholden had been scheduled for election to an American Psychiatric Association fellowship this year and was to have been moderator of the round table on "Frontiers of Psychiatric Research."

Starting his career as a bacteriologist, Dr. Cholden soon became interested in the host as well as in the parasite and furthered his education to receive a degree in medicine. In medicine he found his deepest interest in psychiatry and there exhibited a scope and originality of thought that rapidly brought him to a respected place in the profession.

Dr. Cholden was a man with a continuously questing mind. He was as critical of concepts that he had developed himself as he was of viewpoints that had been advanced by other workers. In one of his last letters he exhibited this foremost quality in a criticism of his own, as yet unpublished, manuscript, "Schizophrenia and the Model Psychoses," written in collaboration with Dr. Charles Savage and appearing in this issue of the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY. No more fitting tribute to his quality both as a person and as an investigator can be written. He remarked:

"For example, one of the things that I feel uncomfortable about in our paper to the JOURNAL OF CLINICAL AND EXPERIMENTAL PSYCHOPATHOLOGY is that I am not so sure about the intensity of the role of anxiety. I feel now, after having done some more work with LSD, that anxiety is not prevalent in all cases. Yet in our papers we say that it is present. I have recently given 175 gamma to a young man who had a reaction to LSD, with no evidence of anxiety except dilation of the pupil. For three hours he was on Wenger's apparatus, which included stomach motility, PGR, finger temperature, axillary temperature, heart rate, blood pressure, etc. There was practically no level of anxiety shown by all of these measurements. Nor did he subjectively feel any anxiety. This, with a sizeable dose of LSD. I have recently given a dose to an alcoholic and have seen no anxiety from the drug itself. This and other things make me question the role of anxiety. I am wondering whether it wouldn't be advisable to rewrite this paper because of my later thoughts associated with anxiety and schizophrenia. I am not sure that anxiety is always present in schizophrenia contrary to public opinion. It seems to me in my latest thinking that there may be two types of schizophrenia. One is an internal preoccupation that maintains itself without internal and external evidence of anxiety. The other is schizophrenia which is so intimately associated with anxiety that is a manifestation of fear of interpersonal relationships."

With Dr. Cholden's tragic death, psychiatry has lost a young and vigorous worker. We have requested and are grateful to be able to include a personal tribute on the following page from his friend and research collaborator of recent years.—*The Editors.*

Just before his death Lou wrote me: "Thank you for your comments about my television show. The response was simply amazing. Enough to supply my narcissistic cravings for the rest of my life." Sad and ironic that this should have been a prophetic statement. Tragic that this show dramatizing the struggle to better the lot of schizophrenics should have been not only the pinnacle but also the end of his career. Impressive as was "Out of Darkness," it was far less impressive than Lou himself. On rounds with Lou, I used to marvel at his majestic command of the situation, his intuitive understanding of schizophrenics, and his interest and devotion. Mute patients had little difficulty in talking in Lou's reassuring presence. In remarkably short time he would have backward patients out of the hospital: patients who had resisted the blandishments of doctors world famous for their success in the treatment of schizophrenics.

Louis Cholden, M.D.

Lou had an enormous vitality and versatility. He began his career as a bacteriologist and physiologist. He did pioneer work on the rehabilitation of the blind and was active in acquainting both lay and professional groups with the problems of the blind. Lou's interest in schizophrenia was stimulated by his work with the Menningers. At the National Institute of Mental Health he began to put into operation some of his theories of the treatment of schizophrenia by giving attention to both the psychologic and biologic aspects of the therapeutic process. He was among the foremost to advocate pharmacodynamic interventions in treatment. He showed a bulldog determination and dedication to the plight of schizophrenics. And he dared to be different.

To love, and to accept death: These are the highest attainments of man. It was easy to love Lou, but not to accept his death. Perhaps Lou is to be envied: how better to die in the full glory of one's achievements. Perhaps a fitting epitaph for Lou is from one of his favorite poems:

> And therefore never send to know for whom the
> Bell tolls; it tolls for thee.

Dr. Charles Savage
National Institute of Mental Health

SYMPOSIUM ON ARTIFICIALLY INDUCED PSYCHOSES

A Historical and Personal Approach to the Development of Experimental Psychiatry

*H. Holland de Jong, M.D.**

OSAWATOMIE, KAN.

Ne demande pas à un savant les secrets de l'Univers qui ne sont pas dans sa vitrine; ca ne l'intéresse pas.—Anatole France.†

Mit dem Wissen wächst der Zweifel.—Goethe.‡

In science, as in art, we may distinguish between two groups: (1) The creators, those proceeding along new pathways, developing new ways of thinking; the discoverers of hitherto unknown facts and relationships . . . comparable to the composers in music. (2) The reproducers, those who apply the discoveries of the first group . . . the members of the orchestra.—H. Holland de Jong.§

It was in 1918, I believe, when I was in the last year of my medical studies, that I made up my mind to become a psychiatrist. My independent thinking caused me to study it my own way. I wanted to start, not at the top but at the basement of the building of psychiatry. At that time Buÿtendÿk had opened a laboratory at the Free University at Amsterdam in The Netherlands for animal psychology, and I requested to work in this laboratory in my spare time. The result was a study of formation of ideas in the dog, which was published in 1919.[1] It was a behavioral study in which Thorndike's method of studying learning ("Trial and Error") in animals was applied to new situations in the dog.[1]

The next year I applied the method to low-grade idiots who were unable to speak. Their reactions were studied in the same way as the dogs' were studied. A miniature of the Thorndike box served the purpose of creating new situations. The dogs worked from the inside of the box, but the human beings worked from the outside. In both cases, a door had to be opened in different positions.[2] In 1921 Jellife, Editor of the *Journal of Nervous and Mental Diseases*, asked me to publish the article on idiocy in his journal.[3]

Later I applied the comparative psychologic method[3] to normal children of and below the speaking age. I separated "paleointelligence" (below the age of 1½ years) from "neointelligence." The second category was defined as the psychologic basis of acting adequately

* Director of Research and Education, Osawatomie State Hospital, Osawatomie, Kan., and lecturer at Kansas University Medical Center, Kansas City, Kan. Deceased.

† Don't ask a scientist about the secrets of the universe which are not of his shop-window; that does not interest him at all.

‡ Doubt grows with knowledge.

§ The Contribution of Holland to the Sciences, New York, The Netherlands' Information Bureau, 1943.

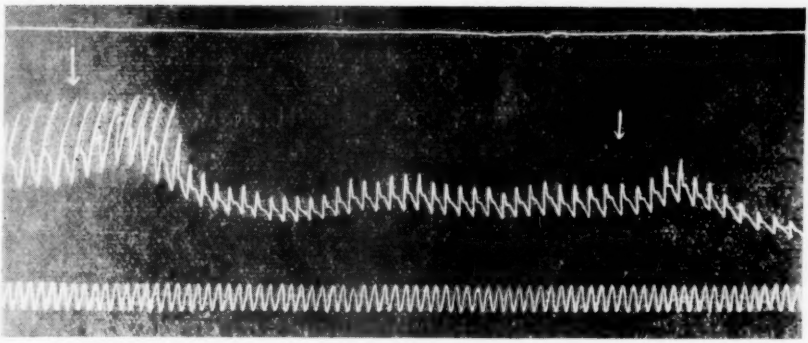


FIG. 1. Normal plethysmogram of an arm (kymographic registration). The white line represents registration of arm movements, the bottom wavy line time. The arrows indicate psychologic or physiologic stimuli such as a demand to calculate 2x2, an "attention" command, or a pin prick. The patient is blindfolded and is not supposed to speak. The figure shows a raise in the tracing after each arrow, followed by lowering of the tracing caused by vasoconstriction.

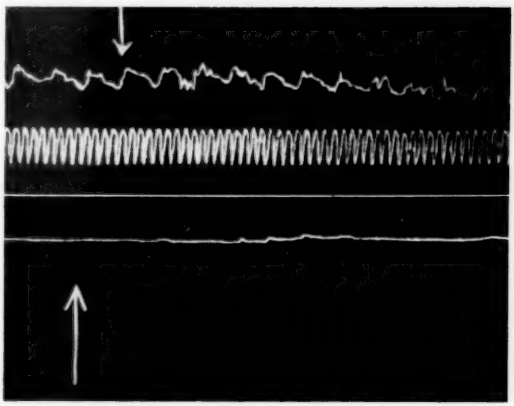


FIG. 2. Plethysmograms of catatonic patients, with arrows indicating stimuli. (Top.) Almost no reaction to stimuli (spastic reaction). (Bottom.) Extreme vasoconstriction and no reaction to stimuli (hyperspastic reaction).

and without trial and error to an entirely new situation, whereas paleointelligence was defined as its opposite.[4]

In 1927 I published the analysis of a case of total agnosia which I considered to be the consequence of a regression to paleointelligence in which the patient could only act under circumstances known long before and was unable to learn anything new.[5]

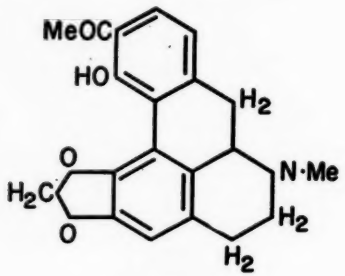
In 1929 an article was published by Baruk and myself in which the neointelligence test, with the replica of the Thorndike box, was applied to schizophrenics. These patients had preserved their neointelligence, even including those who, in appearance, gave the impression of dementia.[6]

In 1920 I had begun a series of plethysmographic studies of normal individuals and psychiatric patients.[7] It was known that physiologic and psychologic stimuli, even of slight degree, brought about changes in the blood volume, e.g., of an arm; however, these changes were irregular. I was able to classify them in such a way that they were interpreted as variations in which there figured an initial increase of volume due to increased heart action, followed by a decrease of volume due to vasoconstriction (fig. 1). However, the state of vascular constriction prevailing before the application of stimuli played an important part in the configuration of the tracings obtained. I divided the reactions into groups, such as, hypospastic, normospastic, and semispastic. An exception was formed by catatonics; they showed no, or hardly any, reaction to the stimuli. This had already been described by Bumke, Kehrer, and Küppers, but I interpreted it as due to hyperspasm (fig. 2). This difference led me to consider the catatonics as a group in which a third factor played a part, and I thought that this could only be interpreted as the interference of an organic, probably biochemical, factor. I came to the hypothesis that the catatonic syndrome (catalepsy, vasoconstriction, pupillary changes) had an organic basis, probably due to pathologic autonomic innervation possibly under the influence of polyglandular dysfunction. It is interesting to note that a variation of this idea was brought up again recently (independently) by Hoffer and Osmond, who regard schizophrenia as an autonomic disease.[8]

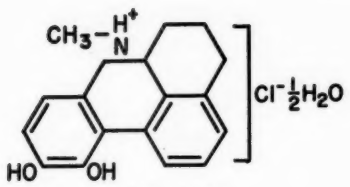
The next step was to try to reproduce this pathologic autonomic innervation on an experimental basis in animals by means of injection of a toxin. If this could be done, the old theory of the toxicity of schizophrenia and catatonia, as given by Kraepelin, Régis, Sérieux, and Jelgersma, would have a scientific basis.

I was so much convinced that it would be possible to reproduce catatonic symptoms in animals that I traveled to several universities in order to ask the advice of different pharmacologists. Finally, Magnus, Professor of Pharmacology at Utrecht University in The Netherlands, advised me to study hashish, but I abandoned this idea after reading an article by Joël and Fränkel.[9] After two weeks a letter arrived from Magnus in which he brought to my attention an article by Frölich and Meyer[10] dealing with a study of muscular contractions of long duration. These authors referred to an article by Peters[11] on a type of catalepsy produced by a certain alkaloid called bulbocapnine (*Corydalis cava*).

The formula of bulbocapnine, as worked out by Gadamer of Marburg, Germany, is:



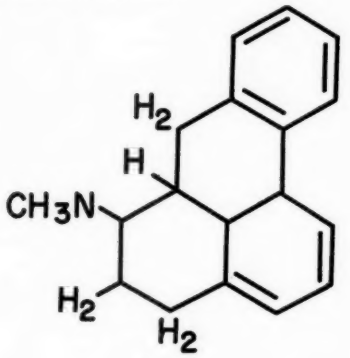
Bulbocapnine



Apomorphine

Bulbocapnine is one of 18 alkaloids of the plant *C. cava*. It is dextrorotatory, whereas apomorphine is levorotatory. The chemical formula of apomorphine is above.

The mother substance of both is aporphine:



Aporphine

In my first attempts with intramuscular injection of bulbocapnine in cats, I thought that the type of active immobility produced by bulbocapnine was not identical with human catalepsy, since the cat's leg could not be extended in space and remain there for a long time. Later I doubted this theory, but at that time I was working in the Neurological Clinic at Amsterdam University and had no opportunity to make a real comparison between the intoxication symptoms of bulbocapnine and the symptoms of human catatonia.

In the meantime, I studied the hypokinetic action of bulbocapnine on tremor of paralysis agitans. It was proved in the work I did with Schaltenbrand from Germany[12] and then with Herman from Boston, Mass.,[13] that bulbocapnine diminished the tremor for about half an hour, that there were refractory cases, and that the action was palliative and not curative. Meanwhile, Schaltenbrand[14] performed, in the laboratory of Magnus, a series of experiments relative to the localization of bulbocapnine effects on different parts of the central nervous system. The conclusion was that bulbocapnine exerted a diffuse action but that for the "acute experiment" the brain cortex was necessary.

In later experiments with Krause from Leipzig, Germany,[15] I found unilateral catalepsy after one-sided ablation of the cerebral cortex in monkeys; however, after a few weeks the

paralytic side of the body also became actively immobile (cataleptic), as shown in suspending the animal by the forelegs on a horizontal rod. Therefore, I concluded that catalepsy could also be produced by subcortical elements substituting for the cortex.

In 1928 I obtained a Rockefeller Fellowship to work in Paris, France. I got in touch with Bourguignon in order to study the chronaxie in cats injected with bulbocapnine,[16, 17] for the study of bulbocapnine still fascinated me. The title of my paper, "Catalepsy and Tremor," which I read before the Paris Neurological Society, indicates that the pendulum of my doubt regarding the interpretation of the bulbocapnine picture had swung back to catalepsy again instead of to the term "cataleptoid state" that I had used before.

At that meeting I met Baruk, and I still remember his words: *"Eh bien monsieur, vous pouvez produire la catalepsie chez des animaux?*"* I answered him in the affirmative, and, when I learned that he had specialized in physiologic and clinical work in catatonics,[18] I realized that fortune had brought me into contact with the man for whom I had been looking. I proposed a mutual comparative study of the effects of bulbocapnine in the cat, as compared with the clinical symptoms of catatonia.

We jointly set up the syndrome of experimental catatonia, consisting of hypokinetic, hyperkinetic, and autonomic phenomena. Hypokinetic phenomena include: (1) diminished motor initiative (hypokinesis), i.e., the impulse to movements and acts is diminished (This may occur to such a degree that the animal remains motionless in a drooping position in one spot for many hours.); (2) catalepsy, which is a variety of diminished motor initiative (The animal assumes positions passively introduced by the examiner. Catalepsy is not only limited to the extremities but is also found in the whole body.); and (3) negativism, a physiologic phenomenon consisting of passive and active resistance to changes of positions already assumed. In contrast to the former group, we are dealing in hyperkinetic phenomena with an abundance of movements, such as running, jumping, etc. There may or may not be a locomotor effect. In the first case, running or jumping results; in the second case, the animal may, for instance, lie on its side and make several rhythmic, stereotyped, or arhythmic movements with the legs. Autonomic phenomena include tachycardia, polypnea, salivation, etc. If one increases the dosages still more, epileptic phenomena occur, and finally death ensues[19]† (see fig. 3 to 5).

It may be of some interest to know that at present I consider catatonia induced in animals by bulbocapnine injection not as completely identical with human catatonia as Baruk and I first thought it was. I now agree with my original idea of 1921. The bulbocapnine picture is identical with postencephalitic catatonia, but I feel again that there is some deviation from the catatonia of dementia praecox. The difference is that catalepsy produced by bulbocapnine seems somewhat exaggerated, whereas in schizophrenic catatonia, catalepsy is more in the background and physiologic negativism is more in the foreground. An experimental picture in which there is the same predominance of negativism over catalepsy is given by injection of mescaline into the monkey, as was first described by us in 1930.[20]

---

* "Well, sir, you are capable of producing catalepsy in animals?"

† A complete bibliography of the work of each of the authors up to that time is included.

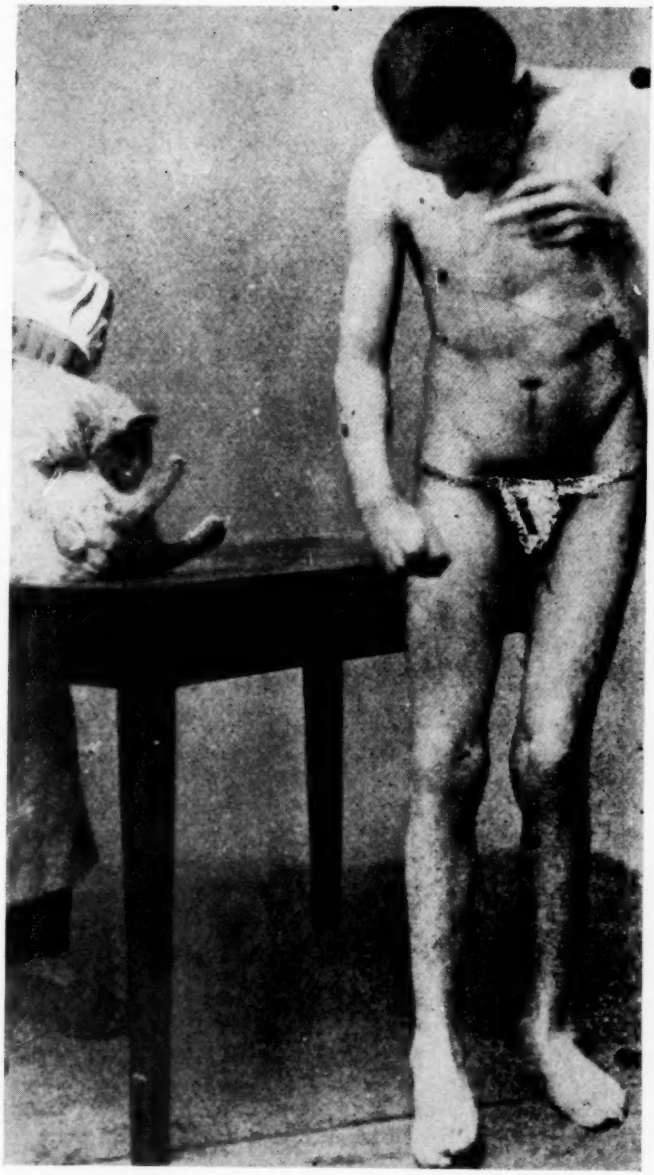


FIG. 3. Catatonic patient and catatonic cat (the cat has been injected with 25 mg. of bulbocapnine hydrochloride/Kg.). Note the curved back in both the patient and the animal. (Reproduced from *La Catatonie Expérimentale par la Bulbocapnine.*[19])

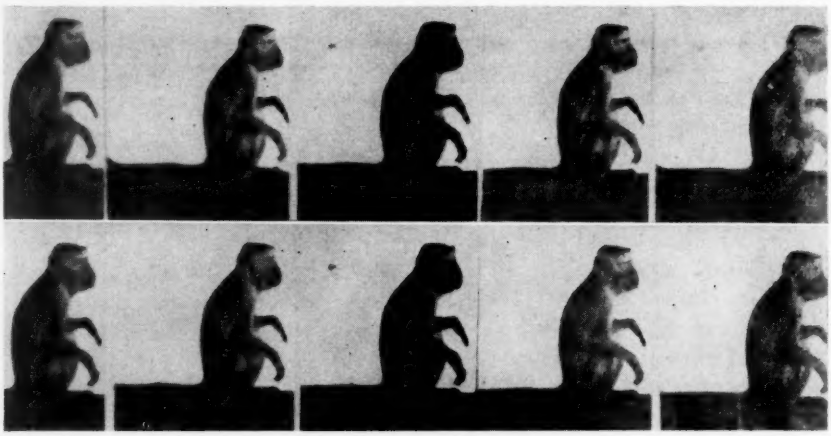


FIG. 4. Active immobility (catalepsy) in a rhesus monkey.

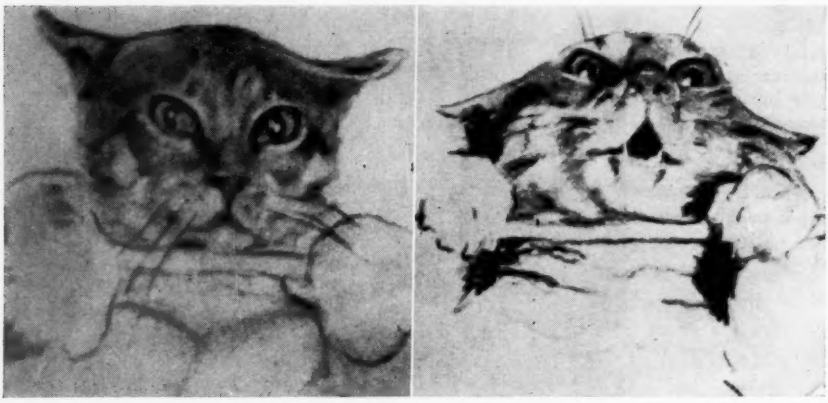
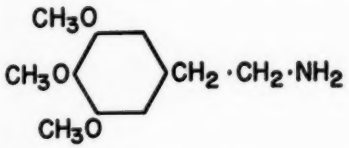


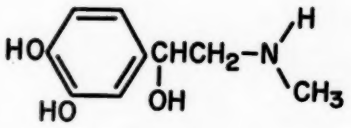
FIG. 5. Alteration of facial expression in a cat injected with bulbocapnine and suspended on a pole. (Left.) Note expression of fear and drooping of both ears. (Right.) Note expression of terror. The cat is howling, as with intense fear. (Reproduced from *Experimental Catatonia. A General Reaction Form of the Central Nervous System and Its Implications for Human Pathology.*[23] Sketches by Helen Chase, formerly of the Psychiatric Institute, New York, N. Y.)

Moreover, other experiments such as Beringer's[21] have shown in men a state resembling a psychosis, with marked hallucinations and autonomic signs such as vomiting, salivation, and mydriasis. The usual doses for men amount to 250 to 500 mg. intramuscularly, whereas a monkey of 2½ Kg. requires a minimum dosage of 270 mg. in order to show catatonic symp-

toms. It is understandable, therefore, that catatonic symptoms have never been produced in men by mescaline, since the doses have been far too small.



Mescaline (Somewhat Related to Epinephrine)*



Epinephrine*

When we combine the findings of former investigations in men and my results with higher dosages in animals, we come to the conclusion that mescaline is capable of producing a psychophysiologic parallelism consisting of hallucinations, autonomic phenomena, and psychomotor symptoms of a type of experimental catatonia in which physiologic negativism predominates over catalepsy. In schizophrenia the same group of symptoms may occur. It has been discussed elsewhere whether the mental symptoms of mescaline injection are identical with those occurring in schizophrenia.[22] All in all, it could be that the combined mescaline picture is very much related to dementia praecox; however, I was careful to state that there is a marked similarity in the principle of the triad of groups of signs and symptoms occurring in schizophrenia and in mescaline intoxication.[20] The criterion of whether an experimental psychosis resembles schizophrenia should always include the fact that psychomotor and autonomic symptoms can be elicited as well as psychopathologic ones.

Hoffer, Director of Research for the Province of Saskatchewan, Canada, writes about this as follows in a letter to Farrar, Managing Editor of the *American Journal of Psychiatry* (Aug. 30, 1955):

> De Jong's first publication, "Proceeding of Royal Academy of Sciences at Amsterdam, 33, 1076, 1930, described an experimental catatonia in animals, especially monkeys, produced by mescaline with a predominance of physiological negativism that resembled human catatonia better than the bulbocapnine catatonia. A discussion of these mescaline experiments appeared in English in De Jong's book "Experimental Catatonia—A General Reaction Form of the Central Nervous System and Its Implications for Human Pathology," Williams and Wilkins, Baltimore, 1945.[23]
>
> De Jong's triad of symptoms which he recognized as the "principle of dementia praecox" did not consist of a combination of autonomic, motoric, and psychomotor phenomena, but was listed as (1) psychopathological phenomena, hallucinations, etc., (2) autonomic signs, (3) psychomotor phenomena in the sense of experimental catatonia. This was the first clear exposition of definition of experimental schizophrenia. At that time, Beringer ("Der Mescalinrausch," Berlin, 1927) had already described systematically the thought disorder and hallucinations produced by mescaline. De Jong added to it psychomotor signs.
>
> It is interesting that although the early works on experimental production of "psychosis" by

* See figure 6 for mescaline-induced catatonia and figures 7 and 8 for epinephrine-induced catatonia.

> chemical means was started in 1920 by De Jong and led to the concept of Experimental Catatonia by De Jong and Baruk in 1930, there was the usual lag of scientific interest which just now has again been revived. At the June meeting of the Society of Biological Psychiatry in Chicago, De Jong demonstrated again that bulbocapnine induced catatonia in humans.
>
> I have written this letter not to be pedantic about literature references but because I feel that pioneers in science deserve adequate recognition of their work. De Jong's concept of the "Catatonizing nucleus" led us in Saskatchewan to the concept of the schizophrenic nucleus which we have postulated may be a quinone indole.

Farrar asked me to answer this letter, which I did in a note to the Editor of the *American Journal of Psychiatry* (November, 1955).

As far as "the usual lag of scientific interest" is concerned, Hoffer is right; a good example of this has been the lag of interest in the first steps of the infant experimental psychiatry, which has now been revived. In the beginning there was great interest from men like Pavlov, Babinski, Foerster, and Adolf Meyer. I was introduced to Pavlov at the International Neurological Congress in Bern, Switzerland, in 1930, where I read a paper, together with Baruk. I spent the whole day with him and his colleagues. As for Babinski, Baruk and I enjoyed his friendship for several years until his death. After my first presentation in 1928 before the Neurological Society of Paris, he had approached asking me to show him the phenomenon of catalepsy in his laboratory. After the demonstration he said he was convinced that catalepsy is a specific psychophysiologic phenomenon. It is an active immobility; a cat can be suspended on a horizontal rod and hold itself there (fig. 5). This proves it is different from paralysis, which is a passive immobility. Also, electromyographic tracings showed me that catatonia induced by bulbocapnine and clinical catatonia display oscillations in flexors and extensors at the same time; Baruk found similar signs in his patients.

Foerster, at that time the leader of German Neurology and neurosurgery, called experimental catatonia one of the greatest discoveries of modern medicine. Adolf Meyer visited me at the Neurological Clinic of the University of Amsterdam, and I gave him a supply of bulbocapnine at his request, the first to be used for experiments in the United States. The work was repeated in many countries all over the world. Furthermore, the Rockefeller Foundation showed its great interest by supplying grants for many years which enabled us to undertake the work on a bigger scale. When I came to the United States in 1940, Gregg enabled me, through another grant, to work at the Psychiatric Institute in New York City. After two years, I was asked by Lyman, at that time Head of the Department of Neuropsychiatry at Duke University in Durham, N. C., to join the faculty as a full-time associate

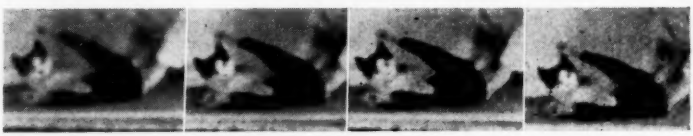


FIG. 6. Catatonia after intramuscular injection of 120 mg. of mescaline sulfate.

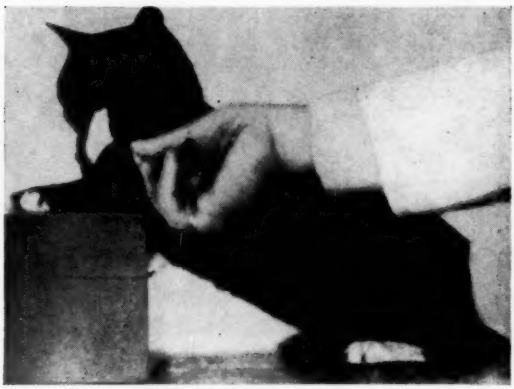


FIG. 7. Catatonia after injection of 10 mg. of epinephrine subcutaneously. The cat is actively immobile and does not move after a flame approaches its whiskers.

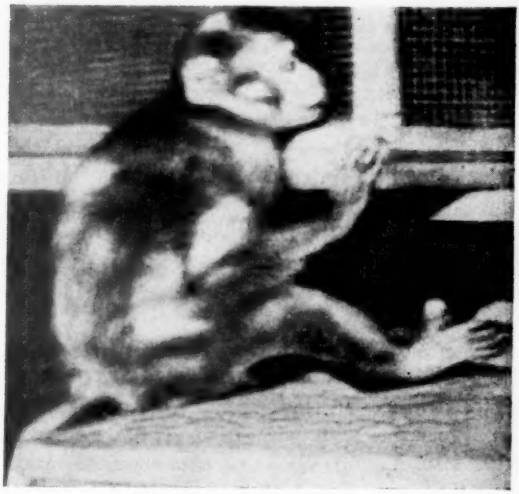


FIG. 8. Catatonic position of a rhesus monkey after a total dosage of 10 mg. of epinephrine were given subcutaneously.

professor for the duration of the war plus one year. After four years, I returned to The Netherlands. However, I soon returned to the United States and then found that the interest in experimental catatonia had virtually disappeared, to be revived only recently, especially by Hoffer.

That was the first phase of the development of experimental catatonia induced by bulbocapnine which I had worked on with Baruk in the animal series. It seemed at that time that those animals without a neocortex did not develop this syndrome whereas those with a neocortex did.

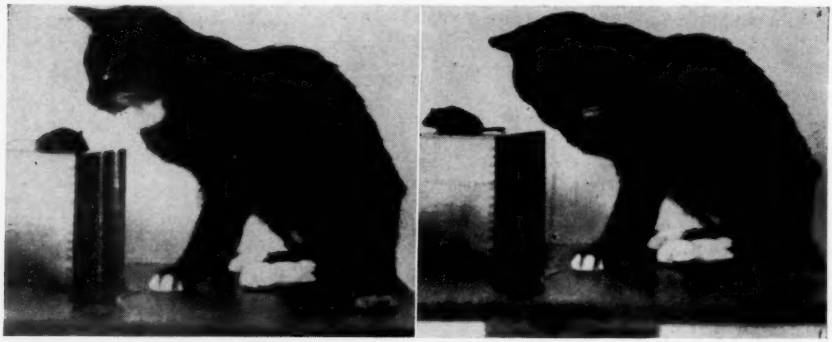


FIG. 9. Catatonic cat and catatonic mouse. Dosage was 0.8 ml. for the cat (1.1 ml. contains 50 mg.) and twice 0.1 mg. for the mouse. (Right.) After 10 minutes the mouse started moving (note the intense salivation of the cat). After 20 minutes, the cat suddenly caught the mouse.

The next phase of our work was done on a larger scale through grants from the Rockefeller Foundation, and with the help of several collaborators on experimental catatonia induced by drugs other than bulbocapnine, in the period of 1930 to 1945. Baruk continued working on the subject in Paris while I worked on it in Amsterdam before 1940 and in the United States after that time. The laboratory for study of pathologic physiology was established as a part of the Neurological Clinic of the University of Amsterdam in 1932. Later it was called the Neuro-Physiological Institute, with myself as Director, and was incorporated into the Neurological Institute, which had the famous Dutch neurologist Brouwer as its Chairman. Some work was also done with Van der Horst in the Valerius Clinic in Amsterdam.

One of our first reflections was whether it would be possible to find the "catatonizing chemical nucleus," starting with mescaline and trying to reduce the simple chemical formula more and more. With the help of several collaborators, we finally found that nitrogen itself could produce catatonic phenomena. Then the question arose as to whether it was nitrogen or the state of asphyxiation that acted chemically as the producer of catatonia. It proved to be the latter. Carbon dioxide, hydrogen, and an oxygen lack in general proved to be capable of producing experimental catatonia. It is interesting to note that, from a completely different viewpoint, our work had converged with that of Baruk[24] and Puech and other co-workers in that vasoconstriction in the brain proved to be present in catatonia induced by bulbocapnine.

It also seems interesting to recall that my plethysmographic work done in 1920 had shown a specific vasoconstriction in catatonic patients.

The drugs other than bulbocapnine and the different ways of producing experimental catatonia proved so numerous that I finally considered the syndrome a general reaction form of the central nervous system. The different ways had no common chemical element;

hypothetically I assumed that cellular oxygen lack was the only common denominator.*

It was proved that the catatonic syndrome could be elicited by: (1) chemical and biochemical means and drugs such as bulbocapnine, cannabis indica, mescaline, hormones (epinephrine, acetylcholine [see fig. 9], and Baruk's *"Catatonie Hypophysaire"*), asphyxia (with gases or bilateral ligation of the carotid artery), urinary extracts, autointoxication (ligation of hepatic artery, Eck's fistula [portal-caval shunt], and ligation of the intestine), nicotine, and the ethylamine indole (the only substance producing a chronic catatonic state); (2) electrical means such as Leduc's current, faradic current, and electroshock (in animals only); (3) different brain lesions of the frontal, parietal, and occipital cortex (maybe only in case of brain swelling); (4) centrifugation; and (5) audiogenic stimulation. To these† may be added the investigations of Baruk who did work‡ on experimental catatonia produced by colibacillosis,[24] tuberculous infection,[25] and bile of patients with infectious hepatitis or schizophrenia.[26]

Recent work at the Osawatomie Research Department was done on bulbocapnine in men.[30] This was first described by the author and Schaltenbrand in 1925[12] after it had been given to numerous patients, Schaltenbrand being the first to have taken it orally. It checked tremors, clonus, and other adventitious movements for about half an hour. It was therefore shown at that time that bulbocapnine given to men had a hypokinetic effect. Henner of Prague[31] used higher dosages, producing signs in the normal individual resembling the encephalitic parkinsonian syndrome but without tremor. My interpretation at the time was that he had produced a catatonic state. De Giacomo[32] injected men intravenously with bulbocapnine and described catalepsy. A moving picture showed the effect of one of our recent experiments with intravenous injection of bulbocapnine in men; our interpretation was that we were dealing with a real catatonic stupor. The patient showed mutism, closed his eyes, responded to talk with a faint smile, and displayed a very typical catalepsy. The catatonic stupor lasted about one hour after the intravenous injection of 150 to 200 mg. of bulbocapnine hydrochloride. At first I called his state cataleptic sleep; however, the pa-

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* This work was done in Amsterdam with F. J. Nieuwenhuyzen (biochemist), D. J. Kok (veterinary surgeon), A. Geesink (surgeon), W. A. den Hartog Jager, and Miss E. Rietmeyer. Other co-workers of the Amsterdam Institute were G. W. Henry and A. Gallinek, New York City; O. Sager, Bucharest, Romania; L. Noteboom and L. van der Horst, Amsterdam; J. Keller, Leipzig, Germany; and F. Krause, Heidelberg, Germany. In the United States my co-workers were Miss E. Chase of the New York State Psychiatric Institute and Hospital, New York City, and E. Stainbrook, W. Brooks, R. Heimburger, J. H. St. John, and Miss L. Sullivan, Duke University Medical School.

† Details on the five ways in which the catatonic syndrome was elicited can be found in my book *Experimental Catatonia. A General Reaction Form of the Central Nervous System and Its Implications for Human Pathology*,[23] which contains the work done in Amsterdam, the Psychiatric Institute in New York City, and Duke University by my collaborators and myself.

‡ A summary of Baruk's separate work is given in his book *Psychiatrie Médicale Physiologique et Experimentale*[27] and *Précis de Psychiatrie*.[24] For studies done in this country on catatonia induced by bulbocapnine, we refer to the work of Ferraro and Barrera and many others. There is also my paper that was read as an opening speech in a section at the International Congress of Psychiatry, Paris, 1950.[28] Baruk was another speaker in the same section and reported on his separate work.[29]

tient, in a recumbent position, kept his arms up in the air for a prolonged time, when brought into this attitude by the examiner. Sleeping patients dropped their arms immediately under the same circumstances. Also, the patient sometimes showed a faint smile when addressed, in contrast to a sleeping person.

The purpose of another group of experiments, especially carried out with the collaboration of Geesink, Nieuwenhuyzen, and Kok in our laboratory, had to do with the following consideration: Since mescaline, bulbocapnine, surgical intervention in the brain, and electrical stimuli to the brain are all procedures alien to the human body, would it be possible to produce circumstances in the body in which toxins might be produced by the body itself? Thus, a great number of experiments were done in order to alter metabolic functions (use of epinephrine and acetylcholine were exceptions to this rule).

Removal of the kidneys, spleen, and several glands of internal secretion, and severing of the blood supply, did not produce any catatonic symptoms in animals. Only if the metabolism were changed through the intestine or liver, did catatonic phenomena occur in the experimental animal. A few examples will illustrate this. 1. Artificial ileus with closure in two places of the small intestine of a dog produced experimental catatonia in 4 of 12 cases. 2. Experimental catatonia occurred after ligation of the hepatic artery in cats. The experimental lesion of the liver was produced by ligation of the hepatic artery proper, or its two branches, as close to the liver as possible. In the beginning of the experiments the animals were operated upon under general anesthesia, afterward under local anesthesia. The latter procedure was adopted in order to avoid the influence of ether on such a richly parenchymatic organ as the liver. The research was conducted in 36 cats, 12 of which, however, can be properly disregarded since they died on the day of operation or shortly thereafter. Of the other 24, 16 showed positive catatonic signs, sometimes for a short time but occasionally permanently. At times the catatonic symptoms were very marked. The post-mortem examination showed vast necrosis of the liver in 14 of the positive cases; in 7 out of 8 negative cases the liver proved to be normal, and, in the remaining case, only a single necrotic spot in the liver was found. 3. Experimental catatonia occurred in dogs with partial elimination of the function of the liver after applying an Eck's fistula (portacaval shunt). Elimination of liver function by means of an Eck's fistula consists of making an anastomosis between the portal vein and the vena cava. After ligating the portal vein close to the liver, the blood flows directly from the portal vein into the vena cava. The blood from the portal vein carrying chemical products from the intestines is conveyed, therefore, into the main blood circulation. It then becomes possible for these chemical products to reach the central nervous system, thus producing neurotoxic symptoms. Eck's fistula had been successfully applied in our institute to 4 dogs by Geesink, who simplified the very difficult method of making the anastomosis between the two vessels.[33] Physiologic observations of these dogs showed that 2 had neurotoxic symptoms that could only be classified as experimental catatonia. The first of the 2 animals showed these symptoms very distinctly for about 10 days; thereafter, the motility became normal again. The second dog showed spontaneous catatonia for about one month off and on; during this period the susceptibility of catatonia from bulbocapnine was enormously increased.

COMMENT

Experimental catatonia is a general reaction form of the central nervous system. It seems that there is no specificity as to etiology, with one exception. In the realm of experimental alteration of metabolic function, a definite specificity occurs, since catatonic signs appear only after partial changes of the function of the intestine and liver.

It is interesting that for a long time the liver has been considered important in connection with mental disease. Hippocrates, Klippel (in 1892),[34] Schryver and Schryver-Hertzberger (in 1924),[35] Claude et al (in 1932),[36] Quastel and Wales (in 1938),[37] and my collaborators and myself (from 1935 to the present) are but some of the men whose work points in this direction. The work of Baruk, Camus, and other collaborators with *"tubage duodenal"* (in 1932),[24] (injection of bile of schizophrenic patients into mice) is especially interesting.

In 1945 in collaboration with St. John, I examined the results of the cephalin-cholesterol flocculation test given to a great number of schizophrenics and found a high percentage of positive reactions.[35] This work was confirmed by many others, for example, Englander and Von Mendelsohn (by oral communications), but contradicted by Zimmerman. In another series I found that especially new patients showed a reaction of more than 2+ after 24 hours. Impressive were 2 patients with a 4+ reaction during catatonic stupor, which disappeared when they recovered after electroshock therapy.

Lately, however, we have rarely found the cephalin flocculation test positive in schizophrenics. There must be an unknown factor.

Other liver tests in schizophrenia are now being done at our laboratory (prothrombin time and other tests, given by Curran and myself). The results are encouraging but are not ready for publication as yet.

It may appear from the above that the author is an organicist; however, this is not true. It seems to me that schizophrenia has a biochemical organic component and a psychogenic one. The former acts in the basement and the latter on the top floors of the same house. Also, schizophrenia seems so complicated that it is difficult to distinguish what is a primary factor and what is secondary. It often seems that when we deal with one etiologic factor, we have caught only one link in a chain.

FUTURE OF SCHIZOPHRENIA RESEARCH

Very close cooperation and integration of different disciplines are indicated. Our present work is organized in this way. We are building up a modest Schizophrenia Institute, incorporated in a state hospital with a biochemical laboratory, which, thanks to the help of the state of Kansas, is being completed and is already in action. So far, we have a research technician and a biochemical consultant visiting us from the University of Kansas Medical Center. In the future, we hope that a small number of patients will be observed in the same building in which the laboratory is situated. We also hope to be able to appoint a full-time staff to help in studying these patients intensively. The author conducts so-called prestaff meetings in which new patients are selected for further studies. An assistant psychiatrist should also re-examine the vast population of the hospital's chronic cases. The

daily oscillations of the clinical picture should be integrated with psychologic and biochemical studies. The staff should be further complemented by a psychologist and a social worker. Research meetings are intended for this integration of different disciplines. The author himself has tried, in his training, to combine several disciplines: clinical psychiatry, clinical neurology, neurophysiology, and even training analysis for a period of a year and a half.

We think that progress in our insight on the etiology of the schizophrenic reaction has been hampered too often by the fact that we have failed to appreciate that the existence of psychopathologic symptoms does not necessarily mean the psychogenesis of these symptoms. Hypothetically, we may assume that a diversity of factors also plays a part in the etiology of schizophrenia, with the difference, of course, that there is no intake of a toxin but that the metabolic disturbance takes its place; here again we do not know which factor is primary or secondary. The lack of interest of one school of thought for the other has to be overcome. We have been through a period of overspecializing in medicine and superspecializing psychiatry. The contempt some psychogenists and certain organicists have for each other is typical of Anatole France's words at the onset of this paper, words of fine irony written half a century ago. It is high time now to overcome this by trying to integrate organic and psychogenic disciplines.

We see in the future schizophrenic institutes all over the world, as there are cancer institutes dispersed over the globe. We are entering a period in which psychoses finally will get the place they deserve in systematic research.

Experimental psychiatry and what I have coined "psychochemistry" (which includes studying chemical effects in an experimental, biochemical, and therapeutic way in psychiatry) will be very important pillars of this work. LSD is in the center of attention at present; the work of Hoffer, Osmond, and collaborators centers on the adrenal gland, as does the work of Hoagland.[39] Our own work, as well as that of others, focuses at present on the liver.

Let us hope that the schizophrenic reaction will not seem to be a general reaction form of the central nervous system as experimental catatonia proved to be. If this should be the case, a very great number of hallucinogens will be discovered without a "schizophrenizing" nucleus, as we have proved that there is no catatonizing nucleus.

We are still in the beginning phase of experimental psychiatry, and, before the problem of the chain of etiologies of schizophrenia and other psychoses can be solved, generations of work lie ahead.

RESUMEN

El autor expone cómo se desarrolló su interés por la psiquiatría experimental y el futuro de la investigación de la esquizofrenia. En su opinión el síndrome catatónico puede ser producido por medios químicos y bioquímicos, y drogas tales como la bulbocapnina y mescalina; por medios eléctricos; diferentes lesiones cerebrales de la corteza frontal, parietal y occipital; centrifugación y estimulación audiogénica. La catatonia experimental es una

forma de reacción general originada en el sistema nervioso central. Parece que no existe especificidad como etiología, con una excepción; en las alteraciones experimentales de las funciones metabólicas ocurre una especificidad definida, ya que los signos catatónicos aparecen sólo después de cambios en las funciones de los intestinos y el hígado.

RESUME

L'auteur discute le développement de son intérêt en psychiatrie expérimentale et l'avenir des recherches sur la schizophrénie. Il croit que le syndrome de la catatonie peut être mis au jour par des moyens chimiques et biochimiques et par des drogues comme la bulbocapnine et la mescaline; moyens électriques; certaines lésions cérébrales du cortex frontal, pariétal et occipital; centrifugation; et stimulation audiogénique. La catatonie expérimentale est une forme de réaction générale du système nerveux central. Il semble n'y avoir aucun signe caractéristique quant à son étiologie, sauf une exception; dans l'altération expérimentale de la fonction métabolique, une particularité définie prend place, puisque des signes de catatonie apparaissent seulement à la suite de changements dans la fonction de l'intestin et du foie.

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Carl Gustav Jung on "The Mind of Man"

Dr. Carl Gustav Jung, participating in the Voice of America's continuing international symposium on "The Frontiers of Knowledge and Humanity's Hopes for the Future," stated that, inasmuch as no psychologically understandable agent has ever been discovered to cause schizophrenia, he now concludes that the illness might have a toxic cause due to an "organic and local breakdown." He stated that physiologic changes take place because the brain cells are subjected to emotional stress beyond their capacity and that experiments with mescaline and related drugs encourage the theory that symptoms of schizophrenia are toxic in origin.

The search for the specific toxin is the task for clinical psychiatry, stated Dr. Jung. And for the psychopathologist and psychiatrist the task ahead is to study the delusions of schizophrenia and their meaning, for "beyond the personally acquired contents of the personal subconscious mind of each of us, there is a deeper stratum—a stratum of the collective unconscious mind of the human race." Research into the problem of the human mind *in toto* is new, but, states Dr. Jung, we now have a real opportunity for increasing our understanding.

Schizophrenia and the Model Psychoses

Charles Savage, M.D., and Louis Cholden, M.D.*

BETHESDA, MD., AND BEVERLY HILLS, CALIF.

The resurgence of interest in the hallucinogenic drugs is intriguing. The ability of drugs to produce psychoses has long been recognized. Descriptions of the effects of peyote (whose active ingredient is mescaline) date back to the sixteenth century.

The scientific investigation of mescaline was begun by Lewin[1] in 1887. The definitive study of mescaline was published by Beringer[2] in 1926. The relationship of mescaline and schizophrenia was suggested by Stockings[3] in 1940. Despite their importance, these studies aroused only sporadic interest. What accounts for the present-day wave of enthusiasm in the scientific world for such studies? One provocative factor was Hofmann's fortuitous discovery in 1943 of the ability of the ergot derivative lysergic acid diethylamide (LSD-25) to produce, in remarkably small doses, a psychotic state phenomenologically akin to schizophrenia.[4] This fulfilled Kraepelin's dream of a psychosis in miniature that would make possible the investigation of the dynamic properties of mental disturbances, which have been so elusive to understanding and treatment. It provided a stimulus for the active and intense interest that has been displayed in scientific laboratories within the past five years. In this reawakening, the properties of mescaline, the prototype of the hallucinogens, are being reinvestigated. In many ways this interest is reminiscent of the development of penicillin, which was rediscovered after antibiotic properties were found in tyrothricin by Dubois and Hotchkiss in 1936. Coincident with the promulgation of Hofmann's discovery was the recognition that substances naturally occurring in the body, such as the adrenal steroids, could produce psychoses. In addition, our scientific disciplines have matured to such a level that psychiatry is now ready for studies in these borderline areas. Many related fields have undergone considerable technical progress. With new insights in pharmacology, physiology, psychology, and sociology, we now have appropriate instruments to properly study and understand the effects of such psychologically potent drugs.

One of the best descriptions of the effect of LSD was given by Hofmann. On the first day that he prepared the water soluble tartrate of LSD he described a peculiar sensation of vertigo and restlessness. "Objects in my vicinity and also the shape of my co-workers in the laboratory appeared to undergo optical changes. I was incapable of concentrating my mind on my work. In a dream-like state I left the laboratory and went home where I was seized by an irresistible urge to lie down and sleep. Daylight was felt as being unpleasantly intense. I drew the curtains and immediately fell into a peculiar state of 'drunkenness' characterized by an exaggerated imagination. With closed eyes, fantastic pictures of extraordinary plasticity and intensive kaleidoscopic colorfulness seemed to surge toward

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The LSD-25 used in this study was obtained through the courtesy of Sandoz Pharmaceuticals, Hanover, N.J.

* National Institute of Mental Health.

me. After two hours this state gradually subsided and I ate dinner with good appetite feeling perfectly normal and fresh."

Hofmann was unaware that he had ingested any of this drug (possibly he had inhaled some of it). A few days later he took 0.25 mg. of LSD orally to study its effect. In 40 minutes he noted slight giddiness, restlessness, difficulty in concentration, visual disturbances, and laughing. He bicycled home with a laboratory assistant. He noticed with dismay that his environment was undergoing progressive changes.

> Everything seemed strange to me and I had the greatest difficulty in expressing myself. My visual fields wavered and everything appeared deformed as in a faulty mirror.
>
> I had the feeling of not getting ahead whereas my escort stated that we were rolling along at a rapid clip. I lost all control of time, space and time became more and more disorganized and I was overcome by the fear that I was going crazy. The worst part of it was that I was clearly aware of my condition, since the mind and power of observation were apparently unimpaired. I was not, however, capable of any willful act to prevent the breakdown of the world around me. . . .
>
> The following symptoms were most marked: 1. Visual disturbances, everything appearing in impossible colors, objects out of proportion. At times the floor seemed to bend underneath and the walls appeared to undulate, sometimes the entire room began to turn, objects close to me seemed far away and objects distant from me seemed to come close and assume frightening dimensions. The faces of the persons present changed into colorful grimaces. 2. Marked motor restlessness alternating with paralysis. Sometimes I moved around the room with exaggerated motions as if I had to remove a horrible demon that had taken possession of me. Then again I lay on the sofa as if paralyzed; limbs and head felt heavy, without feeling, as if filled with lead; I noticed a peculiar metallic taste in my mouth. 3. Suffocating sensation, dry and constricted throat; thought my lungs were paralyzed my heart had stopped. 4. Occasionally I felt as being outside my body. I thought I had died. My "Ego" was suspended somewhere in space and I saw my body lying dead on the sofa. I observed and registered clearly that my "alter-ego" was moving around the room moaning. . . . Everything still seemed to undulate and proportions remained partly out of focus similar to the reflections of a moving surface of water. Everything was submerged in varying unpleasant greenish-blue shades of color. With closed eyes I saw fantastically formed objects passing by in colorful sequence. It was particularly striking how acoustic perceptions, such as the noise of a passing auto, the noise of water gushing from a faucet, or the spoken word was transformed into optical illusion. Every noise and tone was associated with a kaleidoscopically changing picture of forms and color.

This is a classic description of many of the psychic effects of LSD. Similar effects are produced by mescaline. Although Matefi[5] has demonstrated psychologic differences between LSD- and mescaline-induced psychoses, and Cholden, Kurland, and Savage[6] have demonstrated physiologic differences, the psychologic processes are comparable. Some investigators have described mescaline- and LSD-induced psychoses as exogenous toxic states similar to those seen with use of many other drugs. However, there are differences from the ordinary toxic delirium. 1. They are sharply self-limited, seldom lasting beyond 12 hours. 2. There is no clouding of consciousness, as is usually seen with use of exogenous intoxicants. 3. Memory of the event is not clouded or gone after the intoxication is over. Others have stressed the analogy to schizophrenia. Recently Denber and Merlis[7] stated

that mescaline produces "a clinical picture almost indistinguishable from the schizophrenic state." Kauders[8] gave a more cautious statement on the occasion of his introduction of LSD to this country: "LSD may produce in extremely small doses, from 20–40 micrograms, transient psychotic symptoms reminiscent in a certain number of cases of early schizophrenia." Hoch, Cattell, and Pennes[9] state: "One of the most important issues to be clarified is the question—whether the schizophrenic-like psychosis produced by mescaline, LSD and other drugs is the same as the spontaneously occurring schizophrenias or not. The mental picture seen in normals shows features that are frequently observed in schizophrenia. Nevertheless, there are differences, and these in our opinion do not permit an analogy to be drawn between the two conditions." Osmond and Smythies[10] and Rinkel et al[11] believe that mescaline-like or LSD-like substances derived from the adrenals can be postulated as the cause of schizophrenia. They base this postulate on the schizophrenic-like state induced by mescaline or LSD.

Noyes[12] describes schizophrenia as the state in which "... affect seems to be inappropriate, thought to be disorderly, behavior to be regressive and reality to be falsified in the form of hallucinations and delusions. Contributing to the complicating and variable personality disorder is a tendency to the development of disorganizing fantasy states and to an autistic withdrawal of self with a resulting deterioration of habits." He also states: "Perhaps schizophrenia can best be looked upon as a form of adjustment characterized by a withdrawal to an autistic state accompanied by delusional pre-occupations. These processes usually lead to a disorganization of the personality with an impairment of the evaluation of reality." Such a description also applies to the mescaline- and LSD-induced psychoses. However, the only one who is in a position to judge the subjective identity of the two states is a person who has experienced both LSD- or mescaline-induced psychosis and a naturally occurring schizophrenia. Denber and Merlis report such a case: A woman became schizophrenic a fortnight after taking mescaline, and her schizophrenic psychosis was identical with what she had previously experienced with use of mescaline. We know that schizophrenic patients in remission experience an exacerbation of their acute symptoms with LSD and mescaline.[9] In fact, lobotomized patients re-experience prelobotomy symptoms after administration of LSD and mescaline.

The development of an artificial or "model psychosis" that can be studied is not dangerous and is reproducible; it is of short life and is induced at the will of normal volunteers; and it is valuable as an instrument for studying the schizophrenic state, especially since a clear and coherent subjective memory of the experiment allows us to learn more of the schizophrenic-like experience.

We may then have access not only to the dynamics of such a symptom as the paranoid delusion but also to the evaluation of treatment methods of the common psychiatric problem. We know that the use of reasoning and reality confrontation is relatively unsuccessful therapeutically with schizophrenic patients. We have here the opportunity to study the most effective weapons to deal with this disorder in vitro, so to speak, when we study it in a subject receiving LSD or mescaline.

There already has been at least 1 example in which the LSD-induced psychosis was utilized

to further scientific information and psychiatric treatment. Azacyclonol (Frenquel*) was found to inhibit the LSD-induced symptomatology and is now being studied and used for its therapeutic effects on schizophrenic patients. Even if the LSD-induced and schizophrenic psychoses are only symptomatically related, this nevertheless is an important utilization of the similarities for therapeutic purposes.

The discovery of LSD and the investigation of other hallucinogenic drugs have enlarged our own horizons and enriched psychiatry immensely. Nevertheless, to date, experiments with LSD have raised more questions than they have answered: How can such an infinitesimal amount of material so change the psychic life of the subject? Is latent schizophrenia present in everyone, and does LSD merely release it? Is this drug or its derivatives or analogues a metabolic cause of schizophrenia? What are the dimensions of this "other world" described by so many as a result of this drug administration? Is the same psychic experience present for all who take the drugs? Why do some respond with anxiety, fear, projection, and depression, while others sense elation, peace, revelation, and a vision of beauty?

It is not the purpose of this paper to attempt to answer these questions. The authors' purpose is to scrutinize the similarities between the model psychosis and schizophrenia (so often taken for granted) and to point out some of the differences. The data on the model psychosis is obtained entirely from work with normal volunteers who received LSD. The subjects consisted of 10 staff members and 10 volunteers from a religious community. One hundred μg. of LSD were given orally to the staff members and intravenously to the volunteers. Their spontaneous verbal productions were recorded, and their behavior was observed as long as any effect could be noted. Significant differences between the two groups did not appear. However, intravenous injection produced symptoms within 5 to 15 minutes, while oral ingestion produced symptoms in 30 to 60 minutes.

COMPARISON OF REACTIONS AND PROCESSES

The reactions and processes characteristic of LSD-induced psychosis and schizophrenia were: anxiety, perceptual changes, thinking disturbances, mood disturbances, behavior disturbances, ego disturbances, and delusion formation.

Anxiety. A common accompaniment of LSD intoxication is anxiety. It is related to the experimental procedure only to a small degree, since anxiety was shown to be much less when subjects received a placebo, and since repetition of the experimental procedure only partly attenuated the anxiety. There is anticipation of some unknown danger ranging from mild concern to terror. The physiologic effects of LSD seem very close to those invoked by anxiety, and it is difficult for both the subject and observer to determine to what extent the physiologic effects cause the psychic effects, and vice versa.

Anxieties are prominent in the schizophrenic psychosis. Arieti[13] has stated that schizo-

* The trade name of the Wm. S. Merrell Company, Cincinnati, Ohio, for azacyclonol, or α-(4-piperidyl) benzhydrol hydrochloride, is Frenquel.

phrenia is a specific reaction to an extremely severe state of anxiety. "We have seen how an extreme state of anxiety originated in early childhood produces a vulnerability which lasts for the whole life of the individual. We have seen how desperately even heroically the patient attempts to maintain contact with reality and how under certain conditions of stress, his defenses become increasingly inadequate. Confronted with over powering anxiety he finally succumbs and the break with reality occurs." Sometimes the anxiety is not manifest in the schizophrenic or the LSD-induced psychosis. Some schizophrenics give the appearance of happiness, as though they had found the answer to some age-old problem of mankind. Under the influence of LSD, some subjects present a similar picture.

Perceptual Disturbances. These are commonly reported both with the onset of schizophrenia and with the onset of the LSD-induced state. LSD causes changed perception of colors and objects in the immediate vicinity. Everything looks different than before. Luminescence, vividness, and fluorescence are often described. Ordinary spatial configurations are lost, and, with these perceptual changes, the world seems strange, different, and finally unreal. Hallucinations occur in many subjects and are more commonly of the visual type. Subjects describe sounds transfigured into visual patterns. One of our subjects heard Arthur Godfrey on the radio and hallucinated about seeing him on television. Subjects also comment on the menacing appearance of their friends and colleagues.

A patient emerging from an acute schizophrenic episode recalled its onset: "I was walking in the park and everything about me looked differently. Colors became so vivid and strong it is impossible for you to imagine how intense these colors were." Sechehaye's schizophrenic patient[14] describes the first intimation of her disturbed ego state as "illuminated vastness, brilliant light, and the gloss and smoothness of material things." This same patient also complained that people's faces appeared changed. Her playmates looked like lions.

While occasional auditory hallucinations are described, they are unusual in the LSD-induced state. One subject who hoped for a telephone call kept hearing the telephone ring and repeatedly picked up the telephone to answer it. There is rarely a description of hearing voices, which is common in the schizophrenic state.

LSD causes an altered perception of time, which seems endless, infinite, and boundless. Even though subjects know that the effect will be over in a matter of hours, they feel this experience is endless. One subject described standing at the urinal for hours, whereas it was really no longer than a couple of minutes. Similar time disturbances are observed in schizophrenics, who do not adequately distinguish past, present, and future.

Thinking Disturbances. With the onset of the LSD-induced state, thoughts skitter around at a remarkably rapid rate. There is a press of association; a wealth of ideas comes pouring forth. The subject has difficulty concentrating because of the distraction and flood of sensations and associations. Flight of ideas, clang association, and neologisms can be observed; for example, "I wish spring were here, June is Joan, and days are dune, and dune were days." Subjectively the ideas seem richer. Both the subject receiving LSD and the schizophrenic patient are amazed at the revolutionary power of their own thinking. There is a charismatic aspect to the experiences of the LSD-intoxicated and schizophrenic patients,

giving rise to the feeling that they are approaching the truth or gaining a true awareness of the world.

Autistic preoccupation is usually observed with the LSD-induced state. In fact this explains many of the disturbances in concentration, memory, attention, retention, recall, and recognition. This phenomenon is of a degree that is observed with many of our schizophrenic patients. Intermittently a schizophrenic patient or a subject receiving LSD finds that he cannot concentrate or think of anything. He is just "blank." Blocking may be very intense, and this may alternate with florid metaphorical and symbolic thinking. Sometimes different levels of thinking are described; for example, 1 subject, who was aware of lying on the couch, fantasied discussing the chart of a difficult patient on the ward and hallucinated about racing along the highway on a truck and almost hitting a fire engine head on at the curb. All three experiences seemed to him to occur at the same time.

Subjects with LSD intoxication feel the investigator's words are "an intrusion" or at best an irrelevancy. There seems to be a wall between the subject and the investigator: they talk at different levels; they live in different worlds. Every psychiatrist who has dealt with a schizophrenic patient has been confronted by patients who feel exactly this way.

Mood Disturbances. Both elation and depression are seen with LSD intoxication, sometimes in the same subject. Both of these states are also seen in the schizophrenic psychosis. A rather mirthless quality is often characteristic of the laughter of the schizophrenic and of the subject with artificial psychosis; it may turn into tears. The emotional control is relatively poor. Blunting of affect is now recognized as neither a property of schizophrenia nor of artificial psychosis. Where affect seems inappropriate, it is so only in terms of the outer world, not the fantasy state the subject experiences. In deeper levels of intoxication the splitting of affect and content is clearly observed. Some subjects receiving LSD relate horrifying tales and distortions, fear and torment in a bored, monotonous tone of voice, even as do schizophrenics.

Behavior Disturbances. Assaultive and destructive behavior, so frequent in acute schizophrenia, is unusual in the LSD-induced psychosis. However, hyperactivity and restlessness are common. These alternate with abulia and akinesia. Curious behavior patterns with magical overtones are also observed. Regression occurs, but it does not reach the extremes characteristic of schizophrenia.

Ego Disturbances. LSD produces a subjective feeling that things are somehow different, indefinably changed, and eventually unreal. In the less anxious subject there can be wild indulgences in the dream like state of the LSD-induced psychosis. He can take long journeys, create new philosophies of life, talk with God, and be God himself. Subjects often refer to these as daydreams. They may look at the floor and see fish swimming and waves breaking. These experiences may be remarkably satisfying and peaceful and usually take place in those subjects who have very little fear associated with the drug administration and who show little anxiety concerning their sanity. The ego boundaries may suddenly enlarge so that the subject may feel a part of the world, "at one with the desk." (Referring to mescaline Beringer stated: "I felt myself one with the narrow branches of the tree outside; as if I myself were in the voices of the people outside.") Depersonalization and a feeling of sepa-

ration from the body occur. Often the legs are not felt as belonging to the body. They are independent entities, and sometimes subjects will look at them with a great curiosity. Comparable disturbances of the body image in schizophrenia have been described in detail by Schilder.[15]

The LSD disturbances range from a feeling of the unreality of the body, or its parts, to all manners of distortions, including the denial of the existence of the body. One subject said that if she only had a throat she could speak and breathe. Sometimes the body becomes an impersonal object or machine.

Many subjects receiving LSD describe states similar to Sechehaye's patient's description of the beginning of her illness. "At that instance a strange feeling came over me, a feeling hard to analyze but akin to something I was to know well later—a disturbing sense of unreality."

Delusion Formation. Paranoid ideation is a frequent accompaniment of the LSD-induced psychosis. Subjects complain of being observed, spied on, laughed at, and ridiculed. They complain of sexual advances being made to them.

Regressive loss of ego boundaries is characteristic of both the LSD-induced psychosis and the schizophrenic state. Tausk[16] described a schizophrenic girl who laughed when he asked what she was thinking. She thought he was joking. She believed her thoughts occurred simultaneously in her head and in his. One subject who had taken LSD remarked: "Everybody knows I've taken the drug. Everybody is aware of my thoughts." Frank delusions of persecution, such as being converted into or influenced by a machine, so characteristic of schizophrenia, occurred in 25 per cent of our subjects.

DISCUSSION

There are many comparable processes both in schizophrenia and in the model psychosis induced by LSD. Some of the apparent differences are accounted for by the following facts. The LSD subject maintains a double orientation both in the psychosis and in reality. There are constant reminders that he is only being used in an experiment, despite the vividness of the "other world" experience.

The experimental setting is protective and provides many reality supports. Motor activity tends to increase the reality orientations and momentarily dispels the psychosis. This periodic, albeit transient, interruption of the psychosis is usually enough to prevent the development of restitutional symptoms. When the subject no longer is able to recognize that he is only being used in an experiment, the reaction is indistinguishable from schizophrenia. However, only the comparison of the LSD-induced psychosis and schizophrenia can be drawn. An identity cannot be proved at this time. To explain the similarity of schizophrenia and the model psychosis, the following hypotheses may be brought forward.

1. LSD is related to the chemical factor involved in the genesis of naturally occurring schizophrenia. In other words, by chemical means LSD or mescaline produces a schizophrenic reaction.

2. Schizophrenia may be caused by some psychologic disorganization but is maintained

by a metabolic and chemical disturbance that can be mimicked by the administration of LSD or mescaline.

3. The LSD-induced state symptomatically manifests behavioral and experiential responses similar to those in schizophrenia. However, their symptomatic similarities in no way reflect similarities in cause. One might then think of the symptoms of schizophrenia in the same way one thinks of a fever. There are many causes for a fever, and these causes may be markedly different from each other.

4. A rarely considered possibility is that, in the remote and distant recesses of mental life, there is a region in which impaired reality testing, hallucinations, delusions, and misperceptions abound. Both LSD and a series of disease entities entitled schizophrenia activate or bring into consciousness this aspect of the psyche.

Those investigators who are studying the epinephrine oxidation products that may be related to mescaline and LSD are working essentially on the first and second mentioned explanations. Those who have been attempting to understand some psychodynamic responses to be derived from the LSD-induced state which can be related to personality formation and development are working on the last two explanations. It is not yet clear which explanations and investigations will bear the most fruit for our deeper understanding of human functioning.

RESUMEN

Estos autores estiman que, aunque la psicosis inducida por la dietilamida del ácido lisérgico (DAL) y la esquizofrenia se pueden comparar, todavía no se pueden considerar idénticas. Las similitudes pueden explicarse por la hipótesis siguiente: 1. La DAL está relacionada al factor químico relacionado con la génesis de la esquizofrenia que se produce naturalmente. 2. La esquizofrenia se mantiene por un trastorno metabólico y químico que puede remedarse por medio de la administración de DAL o mescalina. 3. El estado inducido por la DAL, se manifiesta sintomáticamente por respuestas de la conducta y experienciales similares a las de la esquizofrenia. 4. Tanto la DAL como la esquizofrenia activan o llevan a la luz de la conciencia una región psíquica en la que se encuentran abandantes fallas de la apreciación de la realidad, alucinaciones, ilusiones y falsas percepciones.

RESUME

Les auteurs croient que, bien qu'il soit possible de comparer la psychose provoquée par le LSD à la schízophrénie, aucune identité n'a été établie jusqu'à présent. Les similarités s'expliquent par les hypothèses suivantes: 1. LSD ressemble au facteur chimique en cause dans la schizophrénie à son début. 2. La schizophrénie se maintient par un trouble métabolique et chimique qui peut être également produit par l'administration du LSD ou de la mescaline. 3. L'état provoqué par le LSD se manifeste symptomatiquement par des réactions de conduite semblables à celles associées à la schizophrénie. 4. Tant le LSD que la schizophrénie activent une région du psyché qui abonde en hallucinations, illusions et réalisme altéré.

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Félix Martí-Ibáñez, M. D., International Editor, Honored

The Editors of *Encyclopedia Americana* have selected Félix Martí-Ibáñez, M.D., Director of the Department of the History of Medicine and Professor of the History of Medicine at New York Medical College, to write the 16,000 word section on the History of Medicine for their new edition which will be published in 1957. Dr. Martí-Ibáñez is the International Editor of the Journal of Clinical and Experimental Psychopathology and Editor-in-Chief of the International Record of Medicine and of the medical newsmagazine MD.

Dr. Martí-Ibáñez was also honored in November by Cuba with the degree of *Commendador*, Order of Carlos J. Finlay. He had been previously decorated in 1954 with the Order of Carlos J. Finlay in recognition of his scientific and educational work in medicine. The Carlos J. Finlay awards were established in honor of the Cuban physician who discovered in 1881 that yellow fever was transmitted by the *Aedes aegypti* mosquito, and they are presented to physicians throughout the world for meritorious achievements in medical science and cultural medicine.

The Response of Normal Men to Lysergic Acid Derivatives (Di-And Mono-Ethyl Amides)*

Correlation of Personality and Drug Reactions

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Considerable interest has been shown recently in the production of an "experimental psychosis"[1] or "schizophrenia-like symptoms"[2] by drugs. Three agents have figured prominently in such reports: mescaline, lysergic acid diethylamide, and lysergic acid ethylamide. The first is derived from the peyote cactus while the latter two are members of the ergot group. The hope underlying this work has been to increase understanding of the psychologic and physiologic factors involved in psychotic states by reproducing such states experimentally in a controlled situation.

This is not a new approach. In 1904, Peters[3] reported on the cataleptic action of bulbocapnine in animals. In 1930 de Jong and Baruk[4] confirmed this observation and studied this drug and related chemicals with reference to their catatonic effect in man. However, progress lagged until the discovery of new chemicals and compounds, notably the three mentioned previously. These have stimulated new work which Rinkel, DeShon, Hyde, and Solomon[2] have hailed as opening a new field of experimental psychiatry.

Experimental work has been interpreted by some to support those views that assume endogenous chemical substances to be the cause of schizophrenia. Thus Rinkel and his associates[2] state, "It may be possible to assume that fundamentally the mechanism of origin of natural and experimental psychotic phenomena is a similar one." Much of the work in this area has been with psychotics or severely disturbed patients. The general conclusion drawn has been that in psychotics the drugs elicit the latent or accentuate the existing schizophrenic symptomatology. Work with normal subjects has been less frequently reported and the predrug individual personality structure in such persons has not been related to the drug effect. This is our principal interest. The present report describes the results following administration of lysergic acid diethylamide to 10 young healthy male subjects and lysergic acid ethylamide to 9 similar volunteers, and the relationship of these results to the personality of the subjects.

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PREVIOUS REPORTS

LYSERGIC ACID DIETHYLAMIDE

Lysergic acid diethylamide and lysergic acid ethylamide are both semisynthetic ergot alkaloid derivatives. Lysergic acid ethylamide[5] differs from lysergic acid diethylamide in having only a single ethyl group, whereas lysergic acid diethylamide has two such groups. The capacity of lysergic acid diethylamide to produce marked psychologic reactions was first observed by Hofmann, who inadvertently inhaled a minute amount while working with the drug and became acutely intoxicated, with great fantasy production. Hofmann's experience led to Stoll's[6, 7] investigations of lysergic acid diethylamide. He reported that the drug produced the most profound psychologic disturbances: hallucinations, compulsive thought and speech, and alteration of consciousness. He regarded this as a psychotic condition and suggested the term "Phantasticum" for the drug. Becker[8] suggested that "Psychoticum" would be more appropriate.

In subsequent investigations[2, 6–12] systemic effects have been reported as similar in both normal and psychopathic subjects; however, a wide range of psychologic effects are described. Unfortunately, it has not always been clear whether descriptions refer to the normal as well as the psychopathic subjects. In general, the following psychologic features have been mentioned. Consciousness and general orientation are reported as maintained, although sometimes clouded. A feeling of "intoxication" is described. Judgment, memory, and other intellectual processes appear to be undiminished. Insight as to the drug origin of the effects is usually maintained and so is "contact with reality." Ideas are variously reported as stimulated with some confusion, or slowed down and inhibited. Along with this is a general reduction in the power of attention and loss of efficiency in concentration. With regard to mood effects, some authors report striking euphoria with manic behavior. Involuntary laughter has commonly been observed. Euphoria is often associated with physical activity, but passive and apathetic euphoric moods are also reported. Depressive reactions are frequently reported. The signs of depression may be associated with tears, resentment, and aggressiveness, or a passive withdrawn or indifferent behavior.

A frequently reported effect is the "wave-like" or periodic and recurrent nature of most of the reactions. Alternate phases of euphoria and depression are also recorded. Early reports stressed the euphoric reaction with an acceleration of mental activity, but later work has revealed more frequent depression and associated "slowing up." Paranoid trends have been described.

Perceptual changes have been emphasized by most workers and "hallucinations" are generally reported. These, however, might better be described as elementary perceptual distortions (perspective changed, shadows and contours fuzzy, with paling of colors) rather than as true hallucinations. In our subjects there was never any loss of contact with the real situation. Upon closing the eyes many subjects have seen flashes of light or lines and sometimes geometric figures, as after mescaline,[1] or have seen figures and objects. Hyperacousia is reported and false interpretation of noises has been found. A few cases of tactile "hallucination," e.g., a sensation of being wet, are described.

The term "depersonalization" is also used by previous authors to denote an assortment of general bodily feelings, for example, heaviness of limbs, limbs seeming longer, numbness, etc. Several writers state that the depersonalization amounts to a true split personality. This is described as of a clearly schizophrenic nature, with subjects feeling that their real self had changed and that they were cut off from the rest of the world.[1, 6–8]

Two workers have carried out Rorschach testing on subjects during lysergic acid diethylamide intoxication. Stoll,[13] reporting on 11 normal adult cases, concludes that the Rorschach changes are typically those of organic deterioration, although some are suggestive of schizophrenia. DeShon, Rinkel, and Solomon,[10] studying 5 normal subjects, concluded that the changes were principally of the schizophrenic or paranoid type.

In general, then, investigators to date have considered the symptoms of lysergic acid diethylamide intoxication as the expression of an acute exogenic psychosis, consisting of a mixture of hypomania in the area of "intention" functions and schizophrenia in the areas of "affect."

Since in psychotics, symptoms tend to be exaggerated, it has been seriously suggested that lysergic acid diethylamide be used as a diagnostic personality test, revealing the cyclothymic as a manic-depressive and the schizoid as a true schizophrene.[7–9] Indeed, it has been recommended to the psychiatrist as an aid in self-analysis, providing him with an experiential sample of his patients' symptoms.[7, 8] There has apparently been some reluctance on the part of therapists so far to avail themselves of this aid.

LYSERGIC ACID ETHYLAMIDE

In 1953, Solms[5] reported on a "new antipsychotic drug with strong sedative effect," lysergic acid ethylamide. In his study of 8 normal men, he reported a triphasic reaction. The first phase (of 15 minutes' duration) consisted of "benign neuro-vegetative irritation" and mild discomfort such as salivation, tears, sweating, ataxia, hyperreflexia, and paresthesias. There was occasional nausea, heavy breathing, and sensation of vibration and tension in the muscles. The second phase (of one to two and a half hours' duration) was one of "psychosis," with a sudden onset of personality changes and simultaneous disappearance of discomfort. The psychopathologic symptoms were primarily those of a schizophrenic-like asthenia, indifference, and intensive phenomena of depersonalization without sleep. Solm's report is, we believe, the only one to date on lysergic acid ethylamide, and contrasts lysergic acid ethylamide with lysergic acid diethylamide. He reports three main differences, but emphasizes that "none of these differences involve questions of principle:"

1. Lysergic acid ethylamide must be given in larger doses (10 times or more) than lysergic acid diethylamide to produce effects.

2. Optic distortions and hallucinations are more frequently seen after lysergic acid diethylamide.

3. Apathy and decreased motivation are more frequent after lysergic acid ethylamide, lack of inhibition and excessive drive being more characteristic of lysergic acid diethylamide.

Solms considers the profound disturbances of the ego to be the basic effect of both drugs

with depersonalization the chief symptom. He states: "It seems to us that such a falling apart of the body-soul unity shows up more frequently and more intensely under lysergic acid ethylamide than under lysergic acid diethylamide."[5]

METHODS AND RESULTS OF PRESENT STUDY

This report deals with the results of administration of lysergic acid diethylamide to 10 healthy male subjects and of lysergic acid ethylamide to 9 similar subjects. Interviews and Rorschach examination of all 10 lysergic acid diethylamide volunteers were obtained both before and during the drug-induced state, and during the nondrug state for 7 of the lysergic acid ethylamide subjects.

I. *Lysergic Acid Diethylamide*

A. *Dose and Route:*

In all instances, lysergic acid diethylamide was given by mouth, in either the fasting state or after a light breakfast. When food was ingested, the time between breakfast and taking of the drug was of sufficient length to make it appear unlikely that absorption was materially affected by the meal. The oral administration of drugs is notoriously less reliable and predictable than the use of parenteral routes, but was adhered to in view of the absence of data on the safety of lysergic acid diethylamide when injected into man. Total doses employed by other authors have varied from 20 gammas[12] to 500 gammas.[14] Most have received 20 to 90 gammas. In our studies, total doses varied from 39 to 86 gammas (most patients receiving one gamma per kilogram of body weight). Thus, both in respect to dose and route, our study is comparable to those previously reported.

B. *"Physical" Effects:*

Changes in vital signs were of slight moment when present and difficult to separate from the changes observed in accommodation with time to a stressful situation, or to increase of ease and rapport with the laboratory personnel, anxiety, or other responses to the effects experienced. With the doses and route employed, cardiorespiratory changes were usually of no consequence in our healthy adult male group. An exception to this statement was observed. In one subject, a tense student with many conflicts, an interview having a mildly probing nature resulted in considerable anxiety during the period following drug administration. Shortly after the anxious state appeared, the subject had a vasomotor disturbance with pallor, cold clammy skin, nonpalpable pulse, slight convulsive movements of the face, and stiffening of the body. (In other studies we have observed a similar state upon injecting a placebo.) The whole episode was over within 30 seconds or so, and was not followed by confusion. The patient had experienced fainting spells before, but had no history of personal or familial epilepsy. Our interpretation of the episode was a syncopal attack (possibly secondary to emotional stress) followed by cerebral ischemia and its manifestations. A subsequent electro-encephalogram on this subject was interpreted as normal.

Giddiness was experienced by 6 subjects, especially on standing. Five subjects had gross tremor of the outstretched hand, with sometimes a subjective feeling of tremulousness. No gross incoordination, ataxia or positive Romberg's sign was evident, although 5 subjects

complained of unsteadiness and decreased coordination. Paresthesias (if one includes all descriptions of numbness, tingling, heaviness, warmth, cold in various parts of the trunk and limbs) were seen in all but 2 of our patients. A curious but very frequent experience was the feeling that these paresthesias would come and go in "waves." Two subjects felt hot or cold or perspired.

Headache or neckache occurred in half of the subjects. Three of the group had vague abdominal or substernal "feelings." One subject had marked and prolonged retching and vomiting following waves of nausea. One subject had an increased desire for food, but said it had no taste for him. Only the subject described previously (under blood pressure changes) became pale. Two subjects complained of a dry mouth. Two subjects felt sleepy, but none actually dozed off.

C. *Mental Effects:*

1. Mood:

Four of our subjects experienced some inner tension or anxiety. Half of the subjects had a mild or marked desire to laugh or were amused without cause, 2 of them actually laughing out loud and smiling for long periods of time, despite an apparent lack of feeling of inner happiness or joy. These 2 subjects described their facial muscles as having an independent, essentially uncontrollable action of their own. Only 2 of the patients had really pleasant, euphoric reactions. One became expansive and experienced a strong sensè of well-being, and another had pleasant bodily sensations with some erotic content. Another subject had marked erotic and pleasant illusions, but mixed with these were anxiety, apprehension, and paranoid trends. No one became really depressed.

2. Thought and Speech Processes:

In our experience there has not been an increase in thought or speech processes (expressed or unexpressed), but rather a slowing down of speech and expression, confusion, difficulty in concentration, and in remembering what has been read or written. One patient observed "increased distractibility." Several have phrased it somewhat differently as "difficulty in paying attention." Eight of the 10 subjects showed this type of response. A possible example of the opposite type of response was one subject who felt that he was speaking a lot more than before, although this was not obvious to the investigators.

3. Perception:

The subjects in our study have not shown any true hallucinations. Three of the subjects had vivid visual illusions, one with markedly erotic and another with somewhat erotic content, but no subject at any time felt that these illusions were real. No other hallucinatory experiences were reported, but several subjects complained that their depth perception seemed to be off, that objects seemed to be indistinct or smaller in size, or that they had persistent after-images. In a few of these latter subjects, a possible explanation for visual disturbances was found in a marked mydriasis which responded sluggishly to light and accommodation. These changes have been reported on occasion by other observers.

4. Miscellaneous:

Some observers have found a tendency for subjects to experience a sensation that they were "outside of themselves." Some of our subjects also stated that at times they seemed

to be "observing someone else doing what they were doing." No real depersonalization, however, was found in any of our subjects.

II. *Lysergic Acid Ethylamide*

A. *Dose and Route:*

Of our group of 9 subjects, 3 were given a total dose of 0.25 mg. and 6 were given 0.5 mg. of lysergic acid ethylamide, all doses being administered subcutaneously. In the only other published report on this drug[5] 8 subjects were given from 0.5 to 0.75 mg.

B. *"Physical" Effects:*

There were no alarming changes in vital signs, although one subject did show a rise in blood pressure from 125/55 to 165/85, in pulse rate from 82 to 130, and in respiratory rate from 18 to 25. Three of the subjects showed no changes in vital signs and one had a slight gradual decrease in blood pressure and pulse over the several hours required for testing (possibly due to inactivity or decrease in predrug anxiety). Most of the subjects (5) have had a transient hypertension, tachycardia, and tachypnea, suggestive of epinephrine release.

Of the "physical" effects, the outstanding ones were nausea (7 subjects, one of whom also vomited), paresthesias (7), dizziness (6), feelings of warmth (3) or cold (1), and salivation (2). In addition, one subject complained of palpitation, one had a transient paroxysm of coughing, and one complained of a sore throat.

C. *Mental Effects:*

The mental change occurring most frequently was a "dulling of the senses," present in 7 of the 9 cases. This was sometimes described as "grogginess," or "a confused feeling." The subjects also complained of difficulty in reading or concentrating. Five of the subjects stated they were sleepy, 4 that they felt "lazy," 5 were "shaky," "apprehensive" or "restless," and 3 had a strange combination of simultaneous energy and lassitude. Two persons described their muscles as relaxed and "rubbery." Two others said they felt "light and buoyant."

The most interesting change observed (in 4 subjects) was a period of hostility with paranoid tendencies.

Three of the subjects considered their reactions pleasant, 3 unpleasant. One of the latter had a panic reaction with intense agitation and overwhelming fear. His reaction was so intense as to require the administration of an intravenous barbiturate. One patient said he had "an overwhelming desire to talk."

Two types of reactions were reminiscent of some responses seen after lysergic acid diethylamide administration: (1) a tendency to feel amused or to laugh out loud (5 subjects), and (2) the description of some symptoms as recurring in "waves." The only finding at all suggestive of the visual illusions so commonly described after lysergic acid diethylamide (and seen in a few of our own subjects who received the latter drug) was observed in one subject who described objects as "looking pallid" and lacking their normal coloration.

RORSCHACH DATA

I. *Lysergic Acid Diethylamide*

All lysergic acid diethylamide subjects were given a second Rorschach examination while

under the effects of drugs. The first Rorschach* examination was given before the drug was administered, as previously described. These tests were given usually several hours after the drug ingestion when the observers believed the symptomatology was either at its peak or just receding. Seven of the 10 subjects showed distinctive changes in the determinants of their responses. (In an extensive study of the so-called ego-depressant drugs, this is the first time we have found a fairly consistent modification of the Rorschach response by the drug.) In 6 of these 7 cases the changes were in the same direction and of similar meaning. In general these changes took the form of an expansive release phenomenon in which the post-drug Rorschach was an exaggerated caricature of the predrug one, whereby previous weakness of ego functions was particularly magnified. Intellectual processes tended to regress to an immature level. Thus animal movement responses (FM) became dominant over human movement responses (M). This was particularly evident where the predrug balance was stable or M not especially dominant. Since M dominance is a normal concomitant of mature development, this reversal indicates regressive and immature thought processes, as well as a weakening of intellectual control over affective and emotional impulsivity. In adults too, the degree of FM dominance correlates with the degree to which productive potential is wasted. The same regressive phenomenon is reflected in the shift in color responses from FC to CF and in a few cases, to C. In adults FC responses should be dominant. They reflect the development in behavior of increased restraint in the regulation of the forms of self-expression, and the modulation and restriction of the behavioral and emotional impulsivity and unpredictability characteristic of younger age groups. These post-drug changes seriously undermined the characteristic mechanisms developed by each personality for the control of behavior and for defense against anxiety. Under these conditions perceptual processes were correspondingly altered with an accentuation of emotional states at the expense of external reality factors. The fact that only 3 subjects of these 7 experienced sensory illusions seems surprising.

The M:ΣC ratio, reflecting the balance of affective and regulatory spheres in the personality (optimally within 2:1 to 1:2 range), was seriously unbalanced under the drug, the median ratio for the 7 cases being 1:3.5 before and 0:7.5 following the drug. This severe threat to self-control was reflected in the experience of tenseness, anxiety, and "jitteriness," as well as the stated fear of losing control.

As indicated above, the degree to which the Rorschach was changed was positively cor-

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* Rorschach scoring used here is based primarily on Klopfer and Kelley.[15] Scoring is in terms of determinants of the response: form (F), movement, human and animal (M and FM), color (C), more or less integrated with form (FC, CF), shading (c) and achromatic color (C′), etc. Interpretation of the determinants is derived from empiric demonstration and from consideration of genetic development. For example, response to color in the cards is empirically related to the initiation of affective experience, and genetically, color responses develop from pure C responses at about 3 years of age to a gradual occurrence and dominance of CF at approximately 6 or 7, followed by a gradual increase of FC responses which normally become dominant over C and CF in the postadolescent period. Interpretation of an individual record depends, however, not only on this rationale, but also upon the context of other determinants in a record. Principles involved have been extensively discussed by Phillips and Smith.[16]

related with the relative weaknesses of personality development already present. Significantly too, the total amount of reaction to the drug (in terms of objective evidence and subjective description) was also highly correlated with a "maladjustment" ranking by the psychologist based on an interview and the predrug Rorschach test. The correlation between these maladjustment rankings and the drug reactivity rankings by the pharmacologist was .93. Rankings by the pharmacologist and by the psychologist were performed independently of course.

Two cases illustrate particularly well the psychosomatic relationships involved. Subject X, already mentioned, who had the syncopal attack, was a chronically driven and tense individual given to compulsive hyperactivity, intellectually, physically, and socially. The reasons for his neurotic manifestations and distinctive defensive mechanisms were not adequately revealed during the predrug interview and testing, but this predrug probing did not result in more than a slight increase in tension and forced jocularity. The predrug Rorschach record of this subject contained only one color response, a pure C. Empirically, pure C responses occur most infrequently in normals, and then only in "impulsive" and "explosive" normals. In the absence of other more mature color responses, pure C responses suggest pathology, possibly of an "organic" nature. After lysergic acid diethylamide, this subject gave four pure color responses of violent fire or blood content. A negative Phillips Fx score,[17] which has been demonstrated to be associated with assaultiveness, was present in the predrug Rorschach (—1.5) and increased postdrug (—5.5). His M:ΣC ratio went from 1:1.5 to 1:6. Seen in these terms, the seizure experienced by this subject is strongly suggestive of an "emergency discharge" of unbearable inner tension, much as the epileptic syndrome probably functions as an emergency outlet in certain constitutionally predisposed individuals.[18]

Subject Y is notable for his vivid and erotic visual "hallucinations:"

12:34 p.m. (Two and a half hours after 60 gammas of lysergic acid diethylamide). Sees dots in round circles (eyes closed). "My face and muscles are twitching—I seem to be talking an awful lot. I don't want to open my eyes, but I don't know why." Sees streaks of wavering gray on ceiling (eyes open). "Oh, it's just the shadow of the blind—it took me a while to figure that out."

12:45 (Eyes closed.) "I see red and green lights like Christmas tree lights against a black background. Opening your eyes brings you back to reality."

12:50 "My eyes are closing as tightly as they can. It feels like cramps. I don't want to open my eyes because I can think freely and it's sort of a mental pleasure—like driving a car at high speed—there's a little Frenchman driving and I'm the passenger."

1:30 Patient given tachistoscopic word perception test. His responses are confused by erotic fantasies visualized when looking into the machine—man and woman kissing, in erotic play, scantily clothed people.

2:30–3:00 Continued sexual images. States fear of having "come off in pants" during images at tachistoscope. Finally feels shorts to see if true (not). "Definite sensation of wet pants."

3:00 Can still see erotic movements, but "I'm all played out." Face feels heavy "as after an enormous drunk. I'm apprehensive after you (psychologist) leave the room. I'm afraid you won't come back. I tremble and sweat. I don't know whether you are testing me or the drug. Maybe it's for my father, or the army or for (college)." Needs considerable reassurance.

Seen in terms of the interview and predrug Rorschach, this subject was immature and

chronically anxious, dominated by sexual fantasies and impulses of a strong homosexual and anal nature. The act of volunteering for the experiment itself had strong "seductive" overtones for him as a possible erotic experience in a guilt free atmosphere. Under the drug these dynamics blossomed out. Rorschach responses demonstrated the collapse of initially weak control functions and defenses.

The content changes in the Rorschach give some example of this:

Predrug	Postdrug
Card IV	
1. Upper part looks like the top view of genitals.	1. X-ray of top of ram's head.
2. Back of a chicken.	2. These wrinkles suggest the end of a penis, these are testicles, they're pretty weird—warped.
	3. Multi-photo of a woman twisting around, arms out at angles.
	4. Faces of women—one looking down askance at other.
	5. Legs—looking up at them.
Card VI	
1. Back of a man.	1. Underneath view of a man with erection—looking up—see the anus, penis—rest of card is flesh.
	2. A black figure in the background—a statue of a man—young, hands at side—it's a little boy of 14 with a pack on his back.
	3. Foot—on its toes.
Card VII.	
1. Back of woman.	1. Don't know whether it's a male or female—looks like the anus.

Superficially, this case is an exception to our Rorschach scoring trends since on the predrug testing he gave three immature color responses and in the posttesting no color responses at all. However, since genetically the period in which no color responses are given precedes the stage at which they are elicited, in this sense the absence of color perhaps represents an even further regression to a lower genetic level than does the shift from mature to immature color responses.

Both of these cases illustrate what seems to be a primary psychologic effect of the drug—the exacerbation of existing symptomatology through a weakening of control functions and defense systems.

II. *Lysergic Acid Ethylamide*

Predrug Rorschach testing and interview were given to 7 of the 9 lysergic acid ethylamide subjects. Again independent ranking by the psychologist and pharmacologist revealed a high correlation (.80) between "maladjustment" and degree of drug "reactivity." The 3 best adjusted individuals (ranks 1, 2, 3) had no, or extremely minor, effects, and this group of subjects did not scatter so widely along the adjustment-maladjustment continuum as did the lysergic acid diethylamide subjects.

The range of reactions and particularly their intermixture in this small sample precludes the analysis of drug reaction and personality structure. However, the 4 subjects who had paranoid or hostile reactions to lysergic acid ethylamide and the single subject responding in like manner to lysergic acid diethylamide deserve special comment, since the reaction has not been seen (when consciousness was unimpaired) in this laboratory during the study of other drugs. An analysis of the predrug Rorschachs (on 4 of the 5) indicates that while none of them could be called "paranoid" (except by analytic implication from homosexual trends in 2 of them) the incidence of "looking," "watching," and "eyes" responses in essentially guarded records is suggestive of suspicious attitudes in interpersonal relations. While this implies psychologic predisposition it is noted that one of these subjects had participated in other drug experiments involving five drugs and this reaction had never been noted. He was, however, atypical in his reactions to several of these drugs, where uniformity of reaction was more common among subjects than in the present experiments.

DISCUSSION

In regard to the comparison of lysergic acid diethylamide and lysergic acid ethylamide, our experiences only partly confirm those of Solms.[5] The doses of lysergic acid ethylamide utilized by us were many times greater than those of lysergic acid diethylamide, but no striking difference in severity of symptoms was seen. This would tend to confirm Solms' statement about differences in potency. Our data on perceptual distortions also suggests that this author's second statement about the rarity of optic "hallucinations" after lysergic acid ethylamide (as compared with lysergic acid diethylamide) is similarly correct. His third differentiation (relative to differential mental effects), however, cannot find confirmation in our data. Both lysergic acid ethylamide and lysergic acid diethylamide seem to produce a general slowing down of mental processes in our subjects. Both drugs show remarkable power in producing definite psychologic changes. While in our experience these changes are not unique and other drugs have, in this laboratory, produced symptoms of even greater degree, the incredibly small traces of lysergic acid diethylamide that are sufficient to effect change is of considerable significance. Those investigators who choose to view these drug reactions as "psychotic" or "schizophrenic" see in this fact considerable support for the conception of schizophrenia as an endotoxicosis. Our own experience with this drug, while limited, does not give much support to such a view since with one exception (suspiciousness) the symptoms observed under this drug are not unlike those produced by other agents and do not, in our estimation, constitute psychotic processes to any greater extent than those produced by other drugs. In this regard it seems important to emphasize the maintenance of voluntary control and, more particularly, of insight and the capacity for reality testing throughout the drug reaction by our subjects.

The relationship of the predrug personality structure and the type of drug reaction was not as apparent with these drugs as with some other we have studied,[19] but the correlation of the amount of induced change and the degree of pre-existing maladjustment implies the presence of significant relationship. This finding suggests McFarland's[20] work on anoxia where he found a high correlation in neurotics between symptom formation, including

physical collapse, and low levels of anoxia (induced by simulated high altitudes) where the normal individual was unaffected.

It is important to keep in mind when evaluating drug reactions that the primary drug changes can constitute a stressful situation for particular individuals and they may react with vigorous restitutive activity.* The complete drug reaction may then be best explained in terms of the individual's defense system or his characteristic reaction to stress or threat in general. The paranoid reactions are a case in point. Thus it might be expected that the poorly adjusted individual would react to drugs with greater diversity and more intensity of behavior than other individuals.

It is easy to appreciate the role of psychologic factors in the "secondary" drug reactions which sometimes supersede the initial, expected one. These reactions are most easily understood as the result of the integrative functions of the personality acting to adjust behavior to an acceptable compromise between internal processes and reality demands or, stated another way, constitute restitutive efforts on the part of a threatened personality organization to preserve its integrity or re-establish its equilibrium. Altering the internal components of this balance may create fear or panic and great efforts may be made to integrate the change in an emotionally acceptable manner. This may be the best explanation of religious revelations following ritual drugs and philosophic formulations during the use of mescaline.

The above situation seems analogous to psychologic defense mechanisms developed as a result of threatening disturbances of intrapsychic mechanisms or interpersonal relationships. The defense mechanism of denial is an example in point. It is an interesting, but unexplained, observation in our drug experiments that denial appears to be most frequently employed by subjects characterized by a psychopathic personality structure. Another observation of this laboratory is that panic or near-panic as a reaction to drugs seems characteristic of personalities struggling with very strong sexual problems, primarily those of a homosexual nature.

The use of drugs to produce a "psychosis in miniature"[1] and to produce secondary defense reactions in order to study experimentally the relationship of defense pattern and its determinants offers interesting possibilities. An extreme example of drug effect on the development and choice of defense mechanism was the reaction of a young college student (following lysergic acid diethylamide) whose integrative efforts during the drug sessions constituted "the most important experience of my life." The "insight" consisted of a decision that "positive action" was the key to interpersonal relations. When first seen (predrug interview), he was characterized by an excessive desire to please and an anxious ingratiating manner. In the interview he was depressed and anxious over his inability to establish himself in peer groups and showed constant preoccupation with the possibility of acquaintances not liking him. As an example of his difficulties he gave his inability to take any side of

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* The fact that many subjects would respond to perceptual alterations and unusual bodily sensations with anxiety is not strange since experimental studies have demonstrated a similar reaction when external cues to depth or distance are altered or made ambiguous.[21]

an issue under discussion for fear of offending one or the other side. Under lysergic acid diethylamide he was frightened by a feeling of waning contact with reality and doubts of the presence of objects. This was mitigated by self-reassuring statements and positive assertions: "That *is* the chair," "The doctor *is* here," and so on. The effectiveness of this restitutive activity was so anxiety-reducing that the subject suddenly saw it as a key to adjustment and happiness. On return to college he put "positive assertion" into action with friends, girls, classes, and the like, and two months later reported himself to be "successful and happy" in everything he had undertaken. Unfortunately, restitutive activity is rarely so effective.

A basic question is whether drugs create something new in the organism or only release that which is already present. In previous study of other drugs[19] we have been impressed with the apparent meaningfulness of the atypical drug reaction in terms of the individual's personality structure and current personal problems. The small sample and the diversity of response to lysergic acid diethylamide and lysergic acid ethylamide obscure such a relationship if it exists here, but the Rorschach changes are suggestive.

Lysergic acid diethylamide has produced greater and more profound changes in the results of Rorschach testing than any other drug we have studied. These changes are not striking conversions of normal to psychotic, but rather consistent expansive exaggerations of the predrug personality in which structural weaknesses and immature factors are magnified. In some individuals already characterized by pathologic signs, such a process may produce a "psychotic" picture. The process itself is better viewed, we believe, as a release of existing tendencies rather than a creation of new elements.

Problems of control and design are especially difficult in drug experimentation, not to speak of "experimental psychiatry," and the ideal is rarely achieved. However, the use of subjects as free as possible of bias and suggestion, of vested interest, is essential. The use as subjects of laboratory staff, doctors, and nurses and others sophisticated as to drugs, especially when the experimental drug is known, may lead to erroneous conclusions. This problem was illustrated by one of the lysergic acid diethylamide volunteers whose visual "hallucinations" were remarkably similar to those of another earlier subject. Striking similarity of personality structure and especially of major personal problems of the two provoked much interest. This interest was greatly lessened, however, when it was discovered that he was the earlier subject's roommate and had discussed in detail his friend's drug reactions before volunteering.

SUMMARY

The reactions of the 10 young healthy male subjects to lysergic acid diethylamide and 9 similar volunteers to lysergic acid ethylamide are described and related to the personality of the subjects. Psychologic interview plus the Rorschach Psychodiagnostic Test were given to all subjects before drug administration and repeated during the height of the reaction to lysergic acid diethylamide. The drugs were administered as unknowns. The following observations were made:

Lysergic Acid Diethylamide

1. Changes in vital signs were of slight moment. Giddiness, tremulousness, and paresthesias were frequent.
2. Mood changes included, commonly, tension or anxiety and desire to laugh without normal cause. Less frequently euphoria and erotic sensations were encountered.
3. Thought and speech processes were slowed down and efficiency impaired.
4. Perceptual changes or visual illusions were produced in half the subjects.
5. Seven of the 10 subjects showed distinctive changes in the postdrug Rorschach, taking the form of an exaggerated caricature of the predrug state in which weaknesses of ego function were further undermined.
6. The degree of Rorschach change, as well as the amount of reaction to the drug, was correlated positively with personality disturbances or maladjustment.

Lysergic Acid Ethylamide

1. Transient hypertension, tachycardia, and tachypnea suggestive of epinephrine release were frequent, as well as paresthesias, dizziness, and nausea.
2. Mental changes were predominantly experienced as dulling of the senses, confusion, shakiness, and apprehension.
3. Four of the 9 subjects became mildly hostile and paranoid. One other experienced acute panic.
4. As with the lysergic acid diethylamide, the degree of drug reaction was positively correlated with personal maladjustment.

The possible usefulness of these drugs in "experimental" psychiatry is discussed.

RESUMEN

Se describen y relatan las reacciones de diez jóvenes del sexo masculino a la dietil-amida del ácido lisérgico (DAL) y de nueve voluntarios del mismo tipo a la etilamida del ácido lisérgico (EAL). Antes de la administración de la droga se hicieron exámenes psicológicos y la prueba del psicodiagnóstico de Rorschach, a todos los jóvenes, repitiéndose los exámenes y la prueba durante el período culminante a la reacción del DAL. Las drogas se administraron sin ser identificadas por los individuos objeto de este estudio.

Los resultados obtenidos dieron lugar a las observaciones siguientes:

DAL

1. Los cambios en los signos vitales fueron de escasa duración. Fueron frecuentes el aturdimiento, temblor y parestesias.
2. Los cambios de humor incluyeron comúnmente, la tensión por angustia y los deseos de reir sin causa justificada. Se observaron con menos frecuencia, euforia y sensaciones eróticas.
3. El pensamiento y los procesos de expresión oral se retardaron disminuyendo su eficiencia.
4. En la mitad de los individuos se presentaron alteraciones de la percepción o ilusiones visuales.

5. Siete de los diez mostraron cambios apreciables en el Rorschach realizado después de la administración de la droga, adoptando la forma de una caricatura exagerada comparados con su estado anterior a la ingestión de la droga, en el cual las funciones debilitadas del yo estaban además alteradas.
6. El grado del cambio del Rorschach, así como el de la reacción a la droga, estaban positivamente correlacionados con los trastornos de la personalidad o desadaptación.

EAL

1. Fueron frecuentes la hipertensión, taquicardia y taquipnea transitorias que sugirieron la liberación de adrenalina, así como las parestesias, vértigos y náuseas.
2. Los cambios mentales predominantes fueron el embotamiento de los sentidos, confusión, agitación y aprehensión.
3. Cuatro de los nueve sujetos se hicieron ligeramente agresivos y paranoicos. Otro experimentó un pánico agudo.
4. Al igual que ocurrió con el DAL, el grado de reacción a la droga estaba positivamente correlacionado con la desadaptación personal.

Se discute la posible utilidad de estas drogas en la psiquiatría "experimental."

RESUME

Les réactions des dix jeunes hommes sains à l'acide lysergique diéthyle amidé et les réactions de neuf volontaires semblables à l'acide lysergique éthyle amidé sont décrites et liées à la personnalité des sujets. Un interview psychologique ainsi que le test psychodiagnostique de Rorschach furent donnés à tous les sujets avant l'administration de la drogue et répétés au point maximum de la réaction à l'acide lysergique diéthyle amidé. Les drogues furent administrées comme inconnues. Les observations suivantes ont été faites:

Acide lysergique diéthyle amidé

(1) Les changements en signes vitaux furent peu importants. L'étourdissement, le tremblement et la paresthésie furent fréquents.
(2) Les changements d'humeur comprenaient généralement la tension ou l'anxiété, et l'envie de rire sans raison. Et moins fréquemment l'euphorie et des sensations érotiques.
(3) La faculté de penser et de parler ralentit et la capacité de bon fonctionnement diminua.
(4) Des changements de la perception ou illusions visuelles se manifestèrent chez la moitié des sujets.
(5) Sept des dix sujets ont accusé des changements distincts au test de Rorschach donné après la drogue, prenant la forme d'une caricature exagérée de l'état avant l'administration de la drogue, au cours desquels la diminution de la fonction de l'égo était détériorée davantage.
(6) Le degré du changement au test de Rorschach, ainsi que le degré de réaction à la drogue étaient liés positivement aux troubles et au déréglage de la personnalité.

Acide lysergique éthyle amidé

(1) L'hypertension temporaire, la tachycardie et la tachypnée rappelant l'effet de

l'adrénaline étaient fréquentes, ainsi que la paresthésie, l'étourdissement et la nausée.

(2) Les changements mentaux se manifestèrent surtout par l'abrutissement des sens, la confusion, le tremblement et l'appréhension.

(3) Quatre des neufs sujets devinrent légèrement hostile et paranoïde. Un autre éprouva une panique sévère.

(4) Tout comme avec l'acide lysergique diéthyle amidé, le degré de réaction à la drogue était en corrélation positive avec le déréglage de la personnalité.

On traite de l'utilité possible de ces drogues en psychiâtrie expérimentale.

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Relationships Between Chemical Structure and Psychoses with the Use of Psychotoxic Substances

"Comparative Pharmacopsychiatric Analysis:" A New Research Method*

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The study of artificial psychoses involves several problems, namely, the question of psychopathologic characteristics or symptomatology, the somatic basis of these psychoses, the difference between inducing and inhibiting chemical compounds, the eventual specificity of psychotoxic effects, the question of relationship of experimental to schizophrenic psychoses, and the like.

Today it is generally admitted that psychotoxic substances do not provoke specific symptoms whether these substances are of a metabolic or pharmacologic nature. All psychotoxic phenomena can be subsumed under the few "acute exogenous reaction types" of Bonhoeffer. According to this author the other existing symptomatologic differences are largely explained by the psychodynamics of the individual, his personal history, his social milieu, and the experimental situation. Nevertheless there are symptomatologic differences that are not sufficiently explained by these factors and therefore other reasons could be involved.

Recently comparative studies of symptomatic psychoses were performed with three half-synthetic ergot derivatives. These compounds are the well-known lysergic acid diethylamide (LSD) and two others with similar chemical structures. It was shown that the psychotic symptoms produced by these substances, even if chemically similar, gave interesting differences. These differences could not be explained by the psychic constitution of the subject, his life history, his psychodynamics, or the experimental situation.

The question arose, therefore, as to whether there existed an eventual relationship between the chemical structure of the psychotropic compounds on the one hand and certain symptomatologic characteristics produced by them on the other.

In the following study, the psychologic effect of LSD was compared with that of lysergic acid monoethylamide (LAE) and lysergic acid amide (LA). We will not concern ourselves here with the individual content of symptoms but only with their formal appearance, that is, the kind and intensity of alterations in perception, consciousness, thinking, mood, etc.

From structural formulas of the three pharmacologic substances, it can be seen (p. 430) that the side chains in each differ. LSD has two ethyl groups on its amide group, whereas LAE has only one ethyl group and LA is not substituted at all.

It is beyond the scope of this paper to describe the order of experiments on all subjects in detail. Fourteen persons, mainly medical men and chemists, were given LAE and LA

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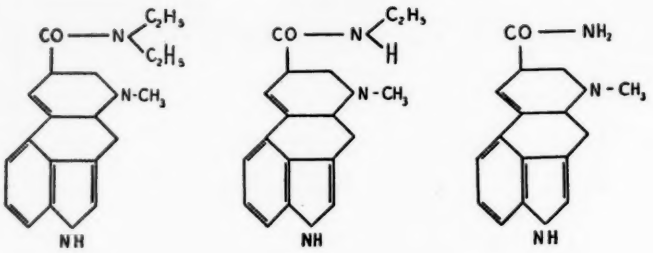
* From the psychiatric clinic of the University of Basel and the University of Bern, Switzerland.



LSD LAE LA

respectively under exactly the same conditions in progressively large doses, and a graded series of 32 psychotic reactions were obtained. It will be shown that the formal aspect of the LAE response is slightly different from that obtained from administration of LA. When LAE was given, the different subjects showed a characteristic psychosis in a rather uniform manner that was striking. With the use of LA, which provokes a slightly different syndrome, the response was also rather uniform. Therefore, and because of considerations of the well-known difficulties of the subjects in repeated experimental psychoses, it was deemed unwarranted to continue administration of LSD on the same persons. The author then compared the results obtained using LAE and LA with the well-analyzed experiments of Stoll and Weyl in which LSD was used. Obviously such a comparison must be done with the greatest prudence, but, since the formal aspects of the responses obtained in the group receiving LSD were also rather uniform, it was deemed somewhat justifiable to compare these data while bearing in mind the aforementioned restrictions. Even then the greatest caution had to be used not to overestimate the results.

1. As is generally well known, the symptomatology of the LSD reaction produced with 25 to 100 gamma given orally or intravenously shows as the most impressive symptom many disturbances in visual perception. (Stoll and Weyl recorded that 56 to 78 per cent with LSD-induced psychoses showed these phenomena.) Much more rare are the perceptual alterations of gustation, audition, and touch. Bodily sensations and changes in body image are seen in almost all subjects. Slight disturbances also occur in thinking as do distortions in the perception of time. Consciousness becomes slightly dreamlike and often leads to certain drowsiness. Self-observation and insight remain intact. Important personality disturbances also occur, namely, feelings of depersonalization and experiences of split personality. There are affective alterations and changes in drive. The subjects often exhibit euphoria, which can change to depression. Furthermore, alterations of the autonomic nervous system appear, especially before the onset of the psychotic phase.

With low doses of LSD the neurovegetative disturbances are paramount; on the other hand, with higher doses hallucinations and the whole psychodynamic personality change predominate. The symptoms begin about one-half hour after administration of the drug and remain intense for a mean of 4 hours. The average total experience lasts 8 hours.

2. The effective dose of LAE is about 10 times as great as that of LSD, showing that it is

more difficult to create optical illusions and hallucinations with LAE than with LSD, even if one considers the big difference between the efficient or working amount of both drugs.

Small doses of LAE produce the same neurovegetative disturbances as do equally small doses of LSD. If LAE is given in a middle range dosage (about 0.5 mg. per injection), it is not the disturbance in visual perception that dominates during the wavelike (up and down) variations in the psychotic symptomatology but rather (in 64 per cent) the phases of extreme abulia, apathy, indifference, and absence of thought ("*Gedankenleere*") with feelings of changed personality, difficulties of contact with the surroundings but rather normal responsiveness, and slight drowsiness, which is stronger than with use of LSD. Sleep however does not occur. Disturbances in visual perception were seen in only 33 per cent; in principle they corresponded to those of LSD but did not seem so intensive or impressive.

One of the subjects described the lethargic phase as follows: "A state of absolute euphoria, of well-being; everything seems to dissolve in the distance, everything becomes unimportant, there is great indifference and difficulty to think and to remember the past. Will power fades away and doesn't react as usual. . . ." Other subjects perceived this state of being overwhelmed and the inability to resist as disagreeable and pressing.

With increasing doses of LAE (about 0.75 to 1.00 mg. and more per injection) the lethargic-apathetic syndrome occurs more often and more intensively (in 83 per cent). The same pertains to the decrease of consciousness and to the optical hallucinations (in 66.5 per cent). Occasionally the latter symptoms can even dominate the picture for a certain time, so that the same phenomena is obtained as with LSD, particularly hallucinations.

This type of high dosage LAE response, identical to the LSD syndrome, was described by a subject as a succession of "images;" such as many friendly lion heads, birds with white feathers, many men with top hats, spider webs, warriors with trumpets, many pelicans, and many peacock feathers. Everything occurred quickly, changed continuously, and had no connection. At the same time the subject noticed everything that happened around him, especially acoustically. It was as though he existed simultaneously in two worlds, one real and the other a dream. He was fascinated by the experience but was slightly indifferent to reality. The symptoms occurred in succeedingly intensive phases. At the same time a tremor in the masticatory muscles was experienced.

There are, then, no principal differences in the mental symptomatology produced by LSD and LAE. Both drugs can bring about the same symptoms, but in general one can say that LAE produces lethargy, indifference, drowsiness, apathy, and abulia more often than does LSD. The deterioration of consciousness is slightly greater with the use of LAE. Finally, the hallucinatory phenomena, which are exceptional with small doses of LAE, become frequent, intensive, and impressive (as always with LSD) with high amounts of LAE.
3. The effective doses of LA are the same as for LAE, but LA induces greater indifference, a decrease in psychomotor activity, and a desire to sleep much more strongly than does LAE, until finally an increased clouding of consciousness produces sleep. LA may provoke sleep after one-half to one hour; if the subject is not awakened, sleep lasts approximately two hours. If the dose of LA is increased, no certain hallucinatory experiences can be noticed, but uncomfortable autonomic disturbances do occur, such as, hypersalivation, emesis,

dizziness and diarrhea; sometimes irritative depressive moods occur concomitantly. Because of these symptoms the tolerance point was considered reached.

With middle to strong doses in 1 subject work became increasingly difficult after 30 minutes. After forty minutes he began yawning and experienced a sensation of inability to use the limbs, a feeling of sinking into nothing, impaired concentration, and an immediate desire to sleep, after which he slept for three hours during the day.

Using the greatest prudence the following provisory interpretations are proposed. If ethyl groups are substituted on the amide group of LA, its power to produce hallucinations seems to increase. On the contrary, if the number of substituted ethyl groups are decreased, hallucinatory potentials are also weakened; i.e., the visual system seems less affected, but psychomotor activity decreases and clouding of consciousness is augmented until sleep occurs.

Of course it remains unsettled as to whether the observed differences in the psychopathologic and psychotoxic effects of LSD, LAE, and LA depend directly on the structural differences of the side chains of the three drugs. This cannot easily be determined. It is not even known how the psychotropic lysergic acid derivatives become effective in the human organism and where they actually function. One is forced to question whether the psychotoxic substance becomes effective through its total structure, or if the psychosis is caused by a result of its breakdown or through the influence of intermediary metabolites. Another possibility is whether the various psychologic responses to these three compounds depend on the differences in the resorptive, metabolic, and excretory processes of the drugs. Or perhaps a chronologic factor may be involved, that is, one substance may metabolize faster than the other, thereby causing psychopathologic differences. There is also some question as to whether these three drugs attack different hypothetical receptors, such as in the brain. Today we have almost no knowledge about the relationship between chemical structure and psychotic symptomatology of psychotoxic compounds. Why, for example, do the hallucinations dominate in 1 case and a clouding of consciousness dominate in the other? What, for instance, are the somatic conditions for the appearance of hallucinations in symptomatic psychoses?

This paper introduces a new procedure to deal with these questions, which we call *comparative pharmacopsychiatric analysis*. By this is understood pharmacopsychiatric research, wherein one works not only with one specifically defined psychotoxic drug but also with additional compounds that are only slightly modified and therefore remain closely related.

SUMMARY

The psychotic reactions produced by three chemically related lysergic acid derivatives show similarities and differences. Their comparison gives some insight into the problems of the relationships between the chemical structure and the psychotic symptomatology with the use of psychotropic drugs and may facilitate understanding of the somatic foundation of symptomatic psychoses.

Since this research method employs a series of slightly modified psychotoxic substances the name *comparative pharmacopsychiatric analysis* is suggested. This procedure is proposed as a new adjunct for study in experimental psychiatry.

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We are indebted to Prof. E. Rothlin, former Director of the Pharmacological Laboratories of the Sandoz Chemical Co., Basel, Switzerland, for providing lysergic acid derivatives.

RESUMEN

La psicosis artificial producida por tres derivados del ácido lisérgico químicamente relacionados, mostró similitudes y diferencias que ayudaron a explicar la relación entre la estructura química y la sintomatología psicótica. Este método de investigación puede constituir una ayuda para mejor entender los fundamentos somáticos de la psicosis sintomática.

RESUME

La comparaison de la symptomatologie des psychoses provoquées par trois dérivés psychotoxiques de l'acide lysergique, apparentés chimiquement, permet de discuter certains rapports entre la structure chimique de la substance psychotrope et l'altération psychotique produite par elle. Et l'auteur propose d'utiliser des substances psychotropes possédant une structure chimique étroitement apparentée pour faciliter l'étude des rapports entre les modifications pathophysiologiques et psychotiques, dans le domaine des psychoses toxiques. Ce nouveau procédé est appelé "analyse pharmacopsychiatrique comparative."

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QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

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Incorporating the International Record of Psychiatry and Neurology

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FOREWORD

The purpose of the QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY is to present promptly brief abstracts, noncritical in character, of the more significant articles in the periodical medical literature of Europe and the Americas.

For readier reference, the abstracts are classified under the following general headings:

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1. Administrative Psychiatry and Legal Aspects of Psychiatry
2. Alcoholism and Drug Addiction
3. Biochemical, Endocrinologic, and Metabolic Aspects
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In fields which are developing as rapidly as are psychiatry and neurology, it is obviously impossible to abstract *all* the articles published—nor would that be desirable, since some of them are of very limited interest or ephemeral in character. The Editorial Board endeavors to select those which appear to make a substantial contribution to psychiatric and neurologic knowledge and which promise to be of some general interest to the readers of the REVIEW. Some articles, highly specialized in character, or concerning a subject already dealt with in an abstract, may be referred to by title only at the end of the respective sections.

A section entitled INTERNATIONAL RECORD OF PSYCHIATRY AND NEUROLOGY is included at the beginning of the journal. The Record Section consists of advanced clinical and experimental reports.

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The Editorial Board at all times welcomes the suggestions and criticisms of the readers of the REVIEW.

WINFRED OVERHOLSER, M.D.
Editor-in-Chief

QUARTERLY REVIEW OF PSYCHIATRY AND NEUROLOGY

*

ABSTRACTS

psychiatry

ADMINISTRATIVE PSYCHIATRY AND LEGAL ASPECTS OF PSYCHIATRY

130. *Some Observations on the Relationship Between Psychiatry and the Law.* THOMAS S. SZASZ, Chicago, Ill. A.M.A. Arch. Neurol. & Psychiat. *75*:297–315, March, 1956.

There is a widespread interest today in applying scientific knowledge to problems of everyday life. Some psychiatrists and psychoanalysts believe that the science of human behavior could be applied to legal matters, particularly to the handling of criminals, in such a way as to make these procedures more humane, more rational, and more just. Others point out how scientific knowledge about human feelings and behavior might also lead to undesirable and dehumanized results.

The author points out that application of scientific knowledge about human feelings, motivation, and behavior is not necessarily beneficial for the individual or for mankind. The basis on which judicial changes are advocated by many psychiatrists rests on concepts that are either ill-defined or borrowed from other areas of thought, e.g., medicine, and can not be applied directly to the social problem of antisocial actions. The two most important concepts in this connection are mental disease and responsibility.

Examination of the problem of responsibility leads to the conclusion that we must distinguish sharply between what happened (causal connection) and what should be done. The term "responsibility" as used in a legal context is therefore very close to meaning punishability. When destructive events occur, there is a search for the responsible party. There are two basic conditions when, in spite of damaging events, no one is held responsible as they were in other times and other cultures: in the case of so-called accidents, such as automobile accidents, and when the offender is a child. The author suggests that our present judgments regarding these matters are based primarily on an (unconscious) identification with the offender. The alternative outcome of the process of identification is that of complete, often aggressive, repudiation, on an unconscious level, of the identification.

Examples of this are seen in the so-called crimes of violence, particularly against children, e.g., kidnaping or killing a child, and in cases of sexual offenses. In these situations the offender is judged responsible, and the meting out of serious punishment is felt to be just.

The psychiatric notion of mental disease as a basis for relative lack of responsibility leads to the conclusion that in actual legal practice increased psychologic maturity would be penalized by greater punishability and, conversely, that offenders judged mentally ill would be afforded protection from punishment without, however, loss of their customary civil rights. If this line of thought is pushed further, the psychologically mature would be an elite class and those less developed would be relatively disenfranchised. It is evident that a thoughtful deliberation of such issues would serve as a necessary safeguard against untoward results that might follow from a hasty and overly enthusiastic application of psychoanalytic principles to legal matters, however passionately these may be advocated in the name of humanism.

Finally, it is suggested that probably the chief unconscious function of the psychiatrist in a court of law consists in taking unto himself a large measure of the guilt that the court (judge, jury, and prosecution) would feel in sentencing (i.e., damaging) an individual. Once there develops a widespread recognition that persons who are mentally ill should not be punished, it becomes necessary for the court to be assured, whenever there is doubt on this score, that it is "playing the game" according to the rules. Accordingly, the psychiatrist is asked to render an opinion as to whether the defendant is sane or not—a judgment that in fact has no meaning other than whether he may be punished with a clear conscience. It would seem that when psychiatrists testify, irrespective of the nature of their testimony, they, in fact, participate in this complex unconscious game of dissipating and projecting feelings of guilt unto others.

According to the traditional psychoanalytic view, the law is considered to be a social analogue of the individual superego and is often viewed specifically as a form of counter aggression pitted against the criminal's aggression. This view is misleading because it places exclusive emphasis on what is probably but one, however significant, facet of this problem. It is suggested that another important function of the law lies in furnishing a social structure by which man can order his relationships with others in such a way that he need not experience an unremitting feeling of (unconscious, unexplained) guilt. By matching his overt behavior against the explicit rules of conduct embodied in the law, he can remind himself that he is innocent. Clearly, this function of the law requires it to be relatively rigid and fixed, in contrast to science, which must be forever tentative and hypothetic. It thus places a conceptual paradox in the way of realizing the ideal of a humanistic law before which each man would be judged on his own "merit." 62 references.—*Author's abstract.*

131. *Delicta during Sleep (Delikte in Schlafzuständen).* VON ALBRECHT LANGELÜDDEKE. Nervenarzt *26*:28–30, Jan. 20, 1955.

The author reports a case in which homosexual relations were attempted while the patient was asleep and another case in which an attack on a supposed intruder was made when the patient was awakened from sleep after he had been drinking liquor. Neither had a definite psychosis, although they showed some personality disturbances. 5 references.

ALCOHOLISM AND DRUG ADDICTION

132. *Alcoholism: Theory, Problem and Challenge. IV. The Treatment of Alcoholism.* KARL M. BOWMAN, San Francisco, Calif. Quart. J. Stud. on Alcohol *17*:318–324, June, 1956.

The present attitude of psychiatry is to regard alcoholism as a symptom of some underlying personality disorder. There is no single alcoholic personality type, and treatment should be altered to fit individual needs. Various theories of causation are discussed, and various methods of treatment are described, including psychotherapy, conditioned reflex therapy, electroshock, and drug therapy with disulfarim, glandular extracts, and tranquilizers. The need for further research is emphasized. 3 references.—*Author's abstract.*

133. *Miltown as a Tranquilizer in the Treatment of Alcohol Addicts.* JOSEPH THIMANN AND JOSEPH W. GAUTHIER, Boston, Mass. Quart. J. Stud. on Alcohol. *17*:19–23, March, 1956.

Clinical reports on meprobamate (Miltown) have shown it to be an effective tranquilizer in anxiety and tension states. As these conditions are prominent in the postalcoholic state, its investigation as an adjuvant to the usual therapy for alcoholism was undertaken.

In the present study, at the Washingtonian Hospital in Boston, meprobamate was administered to 65 hospitalized alcoholics and to 6 drug addicts. Patients were given the drug during the subacute stage, following initial sedation with chloral hydrate, paraldehyde, or insulin. In cases of moderate intoxication, meprobamate was given immediately upon admission. The aim was to relax the patient during the period when tremor, apprehension, guilt feelings, irritability, and sleeplessness were at their worst. The usual dosage was 800 mg. every three or four hours, as required.

Of the 65 alcoholic patients, 5 showed marked improvement. They were substantially relieved of severe anxiety symptoms, and tremors subsided. They slept, ate, and felt well. In 33 additional patients improvement was moderate. Their anxieties were diminished, their mood was improved, and tremors and internal tremulousness were reduced. These patients also slept well, and their appetite improved. An additional 11 patients showed slight improvement. The remaining 16 patients showed no change. These included those who insisted upon deep sedation that would "knock them out." In summary, 75 per cent of 65 alcoholics treated received some benefit from meprobamate during the withdrawal period, including 58 per cent who showed moderate to marked improvement.

The number of drug addicts treated was too small for purposes of evaluation. Interestingly, the 3 patients who showed good response were all addicted to heroin. Of the remaining 3, 2 suffered from a combination of alcohol and drug addiction and the third was addicted solely to barbiturates.

In addition to its administration during hospitalization, meprobamate has also been given to patients upon discharge or during the adjustment period of the night hospitalization plan, to help relieve their tensions and to facilitate the interviews.

Meprobamate appears to be an efficient tranquilizer, without side reactions or aftereffects, in the subacute, withdrawal period. It afforded definite relief from anxiety, agitation, sleeplessness, and tremor in many cases. It has also helped alcoholic patients by relieving

their tensions when they return to their old environment, and in psychotherapy. Apparently, its continued use did not result in habituation. Meprobamate does not appear to affect autonomic balance adversely. Neither does it entail the danger of increasing depression. 11 references. 1 table.—*Author's abstract.*

BIOCHEMICAL, ENDOCRINOLOGIC, AND METABOLIC ASPECTS

134. *Hypnagogic Imagery and Mescaline.* J. AMOR ARDIS AND PETER MC KELLAR, Aberdeen, Scotland. J. Ment. Sc. *102*:22–29, Jan., 1956.

The authors make a comparison of the visual manifestations in mescaline intoxication and in the hypnagogic state. Visual images or "hallucinations" are very typical of mescaline intoxication and are more susceptible to analysis than are other phenomena common to the two states.

In both conditions, the images tend to appear as though projected on a cinema screen and have been likened to a "magic lantern show." They are autonomous, being independent of the subject's volition. Colors tend to be more brilliant than normal and images more vivid than those of ordinary thought or dreams. Altered size of imaged objects is met with (micropsia or macropsia) in both cases; this is reduced by contact with reality, e.g. as the drug wears off or as the hypnagogic image grows older. A certain clarity of detail that seems to transcend the optical limitations of the visual apparatus has impressed both hypnagogic imagers and subjects taking mescaline.

In both instances the images seem to emerge from idio-retinal sensations that most people can, with practice, experience with closed eyes and that have been likened to "luminous dust." Such vague forms may be elaborated into definite patterns, into duplications and reduplications of a particular form (Kluver's polyopia), or into faces, figures, or scenes. Though the relative incidence varies (faces are common in hypnagogic states and rare in mescaline intoxication; the reverse is true of inanimate patterns), individual descriptions bear a marked resemblance. Synesthesias have been encountered in both states, though, again, the relative incidence varies.

Both types of imagery seem to be facilitated by perceptual practice and suitable motivation. Several instances of a summating effect are quoted. In the hypnagogic state and in mescaline intoxication, abstract thinking is not only more difficult but also shows in both cases a bias toward the concrete; this may express itself in the form of symbolic imagery.

There are significant differences in the two states. Auditory and kinesthetic imagery are common hypnagogically and rare in mescaline intoxication. Images associated with mescaline are commonly inanimate and geometric and usually show movement, whereas hypnagogic images are generally of faces or scenes and rarely show movement.

It is suggested that the images of mescaline intoxication and of the hypnagogic state resemble each other in a significant way and that the resemblance points to a common principle: that there is a disorganisation of perception, with a release of primitive responses not normally encountered. The characteristic and dramatic quality is due to the relatively unimpaired consciousness. It may be that a similar disorganisation occurs in certain acute psychotic states.

135. *Adrenocortical Function in Schizophrenia.* EUGENE L. BLISS, CLAUDE J. MIGEON, HARDIN BRANCH, AND LEO T. SAMUELS, Salt Lake City, Utah. Am. J. Psychiat. *112*:358–365, November, 1955.

The 26 patients selected for study had chronic schizophrenia, principally of the hebephrenic type. All had been in the state hospital for five years, and, with the exception of 3, all had received insulin and electroshock therapy during this period without significant benefit. No individual was included who was malnourished; the subjects ranged in age from 20 to 45 years. It seemed likely that any disturbance in adrenocortical function, if it be characteristic of schizophrenia, would be evident in such a group. The concentration of adrenal steroids (17-hydroxycorticosteroids) in the peripheral blood was determined at 8 a.m., after the intravenous administration of various amounts of corticotropin or of a pyrogenic substance, and after the subcutaneous injection of regular insulin. Similar studies were made on a comparable group of normal subjects. The adrenocortical and pituitary-adrenocortical reactivities of chronic schizophrenic and normal subjects were equivalent. There was no evidence of any impairment of adrenocortical physiology in the chronic schizophrenic patient. 46 references. 4 figures. 4 tables.—*Author's abstract.*

CLINICAL PSYCHIATRY

136. *Symptom-Picture of Cyclothymic Mania in Different Age Groups (Uber das alterseigentümliche Erscheinungs bild der Zyklothymen Manie).* W. ZEH, Cologne, Germany. Fortschr. d. Neurol., Psychiat. *24*:434, Aug., 1956.

The symptoms of cyclothymic mania are described according to age groups. The author distinguishes the mania of middle aged persons who show a clearly outlined picture of the mania of maturity and the mania of regression, characterized by deep mood swings and emotional upsets. The empty rigid mania of old age is accompanied with more or less evident organic symptoms. The mania of adolescence often shows a slightly differentiated picture due to puberty, teenage behavior or signs being similar to catatonia; therefore it is difficult at times to distinguish them from abnormal emotional reactions and hebephrenic processes. However, they too do not show genuine schizophrenic symptoms.

137. *Atypical Forms of Schizophrenia (Formas atípicas de esquizofrenia).* A. SAAVEDRA, Lima, Peru. Rev. neuro-psiquiat. *19*:1–97, March, 1956.

The concept of schizophrenia is reviewed and the notion of process and the diverse etiopathogenic theories analyzed. Emphasis is placed on the so-called fundamental characteristics of schizophrenia. The work is based on observation of 20 atypical forms, namely, seven endoreactive and 13 atypical proper.

The endoreactive forms, considered as a new variety of schizophrenia, have the following particularities. 1. They appear after prolonged adverse environmental influences. 2. There is a change in the fundamental mood. 3. Dysthymia is seen in clear consciousness. 4. Inversion of affect occurs with propensity to the anticonventional and heterogeneous, irregular, and unpredictable behavior. 5. Vegetative reactions are marked. 6. Slight de-

terioration takes place. 7. The forms are resistant to biologic and psychologic treatments. 8. Most of the symptoms are episodic and alternate with periods of apparent normality, especially in a new social setting; life in the family circle, however, is almost impossible.

Three groups are considered in the atypical forms. 1. Two pseudoneurotic forms begin with hysteria and hypochondriasis, and later schizophrenic symptoms (hebephrenia, paranoia, and catatonia) develop. The hebephrenic form predominates in cases in which hysteria occurs at the onset. 2. Forms with endocrine disturbances, 1 case of schizophrenia of the catatonic-paranoid type, and 1 case of menstrual symptomatic psychosis, which was exceedingly prolonged during the third episode and which was similar to the evolution of the schizophrenic process were regarded as atypical. 3. Forms that adopt the physiognomy of onset of other endogenous psychoses are the manic-depressive and epileptic states, in which the genealogic tree has a charged top corresponding to these psychoses, making the schizophrenic pattern atypical.

138. *Neuropsychiatric Sequelae of Prematurity: A Longitudinal Study.* HILDA KNOBLOCH, ROWLAND RIDER, PAUL HARPER, AND BENJAMIN PASAMANICK, Baltimore, Md. J. A. M. A. *161*:581–585, June 16, 1956.

In order to study the effects of prematurity on development, a Gesell Developmental Examination and a physical examination were given to a group of 992 infants in Baltimore. In this group were 500 single-born premature infants and 492 full-term control infants; the latter were matched to the premature infants on the basis of race, season of birth, parity of the mother, hospital of birth, and socioeconomic status of the parents. All socioeconomic groups were included, and 85 per cent of the infants completed all examinations scheduled. Analysis of the findings shows that no significant difference was noted between white and nonwhite subjects in the incidence of neurologic and intellectual defect when adjustment was made for differences in weight. The incidence of abnormality increases as the birth weight decreases. At 40 weeks of age, when the rate in the total premature population is adjusted according to the expected weight of the surviving premature infants, the expected over-all incidence of serious neurologic abnormality (possible cerebral palsy plus overt neurologic defect) is 8.4 per cent, significantly higher than the rate of 1.6 per cent in the control subjects. For mental deficiency (borderline defective, defective, and defect of a type unclassified) the expected rate is 2.6 per cent, not significantly higher than the rate of 1.6 per cent in the full-term subjects, although in the same direction. Of the infants with a birth weight of less than 1501 Gm. 50.9 per cent have neurologic or intellectual defect. Some of these also have a major visual handicap. The adjusted percentage of premature subjects who show some departure from normal development is 25.7 per cent; of the full-term control subjects the departure is 12.8 per cent. 10 references. 4 tables.—*Author's abstract.*

139. *The Psychology of Depression and Its Management.* MORTIMER OSTOW, New York, N. Y. Bull. New York Acad. Med. *31*:757–773, October, 1955.

Depression is an affect that appears either in response to the loss of a love object or in anticipation of some act that would result in the loss of a love object. The characteristic

psychic and physical components of the depression syndrome can be understood as devices to compel protective acts on the part of those who love the patient. When depression follows an externally imposed significant loss, it may be considered normal. When it follows no loss or a trivial loss, it is pathologic. In such a case, the depression is provoked by the unconscious fantasy that a wish to destroy or injure the love object has been realized. However, the ensuing depression is usually not successful in terminating the hostile tendency that continues to express itself against love objects in passive and indirect ways and, because of the guilt that the aggression evokes, reflexively in self-destruction.

Depression drives the process of dissolution of ties in such a way that something of the lost object remains by means of a process of identification. Normal depression requires no treatment and neither can nor should be circumvented. The management of abnormal depression depends upon such factors as danger of suicide, accessibility of the patient to psychotherapy, the presence of contraindications to electroshock therapy, and the chronicity of the depression. In general, abnormal depression is most rapidly dissipated by electroshock therapy, while the propensity to recurrent depressions and the interval neurotic personality will be most effectively treated by psychoanalysis.—*Author's abstract.*

140. *The Reliability of Psychiatric, and the Validity of Psychological, Diagnoses.* G. A. FOULDS, Essex, England. J. Ment. Sc. *101*:851–861, October, 1955.

Thirty-six successive admissions were diagnosed independently by two psychiatrists and one psychologist. The diagnosis of the psychologist was based on a short test battery administered by himself in 18 cases and by a colleague in 18. In addition, a psychiatrist and a psychologist "guessed" the diagnosis on the basis of knowledge of the patient's age and the ward to which he or she was admitted.

A diagnostic agreement scale, ranging from complete agreement on major diagnosis and features (6 points) to complete disagreement (0), was constructed.

The two psychiatrists and the psychologist were more or less equally successful in reaching agreement among themselves at a level well above that achieved by the "guessers."

The final psychiatric diagnosis was reached after discussion between the two psychiatrists. The agreement between the psychologist's initial diagnosis and the final psychiatric diagnosis was significantly higher (at least at the 1 per cent level of confidence) than between either "guesser" and the final psychiatric diagnosis. The psychologist was not significantly less successful when he did not see the patient.

In the setting of this investigation it would appear that the reliability of psychiatric, and the validity of psychologic, diagnoses are not as poor as current opinion (unbacked by adequate experimentation) would lead one to suppose. 15 references. 8 tables.—*Author's abstract.*

141. *Domiciliary Consultation in Psychiatric Practice; Analysis of 1000 Visits.* DENIS LEIGH, London, England. Lancet 2:1285–1286, Dec. 17, 1955.

Since the introduction of the National Health Service in Great Britain, it has been possible to arrange consultations with specialists in cases of urgency in the patient's home. The family doctor may choose any specialist and request him to make a visit. There is no

obligation on the part of the specialist to make a visit, the arrangements being identical to those obtaining in private practice. In the period from 1949 to 1954, over 1000 visits were made to patients presenting as psychiatric emergencies. These domiciliary visits represent a real advance in three respects: (1) The patient is seen in his own social setting, and his fears and prejudices against psychiatrists are often allayed. In 90 per cent of the cases, treatment or advice was possible on an entirely voluntary basis. (2) The visit helps to develop and cement relationships between family doctor and specialist. (3) The psychiatrist is brought out of his institution into the outside world.

The diagnostic grouping varied little from year to year. About one third of the patients were suffering from a depressive illness and nearly one third from a neurosis. Organic disorders comprised nearly one fifth of the cases, a very important finding carrying the implication that a sound training in medicine is essential for the psychiatrist.

The depressive illnesses, in particular the suicidal threat, clearly present the family doctor with the bulk of his acute psychiatric problems. Instead of being taught a psychiatry based on controversial psychologic theory, as a student, attention should be concentrated on descriptive clinical psychiatry.

General practice is not the milieu to practice other than a supportive type of psychotherapy.

The potentialities of a domiciliary service have not been fully developed. Apart from a purely consultative service, it may be possible to develop a home care service. The future organization of the psychiatric service will develop with the provision of outpatient and day hospital facilities, and every effort should be made to keep the psychiatric patient in touch with his own milieu. Any measure that avoids the admission of a patient to hospital and yet provides the same, if not better, patient care will be worth developing. 10 references. 3 tables.—*Author's abstract.*

142. *Effects of Partial Perceptual Isolation in Mentally Disturbed Individuals.* H. AZIMA AND FERN J. CRAMER, Montreal, Canada. Dis. Nerv. System *17*:117–122, April, 1956.

The disorganizing effects of sensory isolation on animals and normal human subjects led the authors to study this problem in mental patients for the purpose of gaining some information about the therapeutic value of the disorganization-reorganization sequence of the psychic events and about the problem of depersonalization and body schema.

Two persons suffering from hebephrenia, 5 from depression, 2 from obsessive neuroses, and 5 from neurotic anxiety states were subjected to partial sensory and expressive isolation for an average period of four days.

Two sets of changes occurred, namely, disorganization and reorganization. Disorganization consisted of the appearance of a depersonalization state in 8 patients, of visual, auditory, and gustatory hallucinoses, and of paresthesia; in the 2 persons with obsessional neuroses acute psychotic episodes developed, and they were treated with electric shock. Reorganization consisted of marked change in mood in almost all of the depressed patients, 2 of whom showed lasting recovery and were discharged without any other therapy. In addition, constructive aggression occurred in most patients with an increasing tendency to socialization and relationship undertaking.

The common emergent dynamic process during isolation which was concomitant with

the change in body schema was found to be related to the quantity and direction of aggressive tendencies. It appeared that repression and aggression turned against the self led to the depersonalization syndrome. The theoretic aspects of the problem are discussed and physiologic, relationship, and psychologic hypotheses outlined. 34 references.—*Author's abstract.*

For Reference

143. *Review of Neuropsychiatry, 1955.* STANLEY COBB, Cambridge, Mass. A. M. A. Arch. Int. Med. *97*:610–617, May, 1956.

GERIATRICS

144. *Prognosis in Psychiatric Disorders of the Elderly: An Attempt to Define Indicators of Early Death and Early Recovery.* D. W. K. KAY, VERA NORRIS, AND FELIX POST, London, England. J. Ment. Sc. *102*:129–140, Jan., 1956.

A study was made of 229 patients of more than 60 years of age who were admitted to a mental observation unit in London with the intention of finding which clinical characteristics observed during 10 days of admission were useful in predicting the outcome of the patient's condition. The main clinical and environmental features of each patient were recorded, and two clinical investigators committed themselves to predictions respecting survival and duration of stay in the mental hospital. The criteria chosen did not enable the clinicians to predict reliably which patients would die or which would make a social recovery within three months. They forecast the death of 97 persons within one year and the survival of 120 for at least one year; of the former, 82 persons died (80 per cent) and of the latter, 102 (85 per cent) survived. The clinicians were right in 85 per cent of the cases in predicting those patients who would survive and be discharged from the hospital within one year and those who would not.

From the results of this study it was possible to formulate a number of prognostic indicators that would have been more successful in predicting the outcome within three months than were those initially used by the investigators. Three factors in particular were predictive of early death, namely, advanced age (at least 80 years), focal lesions of the central nervous system, and psycho-organic without functional symptoms. There were five factors that were associated with the unlikelihood of social recovery within three months, namely, advanced age (at least 70 years), focal lesions of the central nervous system, psycho-organic without functional symptoms, social isolation, and no previous history of mental illness. Survival and recovery rates within three months of admission were inversely proportionate to the number of unfavorable prognostic indicators present in each case.

The results of this study suggest that when suitable disposal of large numbers of elderly patients is at issue, fewer errors are likely to be made if certain characteristics that affect the outcome unfavorably are adequately taken into account. Those defined above are relatively easy to assess after only a short period of observation (as little as 10 days). In circumstances in which provision of inpatient facilities for elderly patients is inadequate to the demand, an early selection of patients who are most likely to recover from the current attack of mental disorder and who would therefore benefit greatly by transfer to hospitals

providing modern psychiatric treatment is a goal worthy of attainment. 6 references, 3 tables.—*Author's abstract.*

145. *Improving Senile Behavior with Reserpine and Ritalin: New Approach with Use of Methyl Phenylpiperidylacetate.* JOHN T. FERGUSON AND WILLIAM H. FUNDERBURK, Traverse City, Mich. J.A.M.A. *160*:259–263, Jan. 28, 1956.

The authors evaluated the effectiveness of reserpine and methyl phenylpiperidylacetate, a psychoanaleptic drug, in controlling, ameliorating, or eliminating the abnormal behavior manifestations in elderly hospitalized patients. This report covers the authors' observations after approximately 11 months of orally administering the drugs to 215 female patients, more than 60 years of age, who were management problems due to one or more manifestations of abnormal behavior. The ages of the 215 patients ranged from 60 to 84 years, with the average being a little more than 66 years. The length of time each had been in the hospital varied from 1 to more than 53 years, with the average time of 18 years.

The first dosages given were based on an evaluation of the individual's behavior. This was accomplished by using a check system, which covered the following 11 points: personal appearance, personal care, motor activity, aggressiveness, eating habits, toilet habits, night behavior, socialization, supervision needed, cooperation in routine, and rehabilitation. Those patients showing predominance of overactivity in these categories were started on therapy with reserpine 0.25 mg. three times a day; those showing a predominance of negative characteristics were started on therapy with methyl phenylpiperidylacetate, 10 mg. three times a day; and those showing a mixed type of behavior were started on therapy with both drugs at the same time, 0.2 mg. of reserpine and 10 mg. of methyl phenylpiperidylacetate, three times a day.

After a period varying from three days to three weeks, 57 of the 62 receiving methyl phenylpiperidylacetate alone and 116 of the 131 receiving reserpine alone were given the other drug. Reserpine was added at the rate of 0.1 mg. three times a day and methyl phenylpiperidylacetate, 5 mg. three times a day. As the clinical behavior pattern of each patient shifted toward normal, the dosage was changed, based on individual improvement and the amount of overactivity or underactivity present. By this method, after periods varying from four to eight months, the authors have been able to discontinue use of the drugs completely in 67 of the 215, without a return of the original abnormal behavior. The other patients have had their medicaments discontinued one or more times during the 11 months of the project, but, in order to maintain the optimal improvement, it has been necessary to continue use of the drugs in these 148. At the time of writing, 136 are receiving 0.1 to 0.2 mg. of reserpine and 5 to 10 mg. of methyl phenylpiperidylacetate three times a day, 8, 0.5 to 1.0 mg. of reserpine and 5 mg. of methyl phenylpiperidylacetate, and 4, 0.2 mg. of reserpine and 20 mg. of methyl phenylpiperidylacetate.

The improvement was striking. Effects were sufficiently prompt to permit control of behavior by adjusting dosages and supplementing one drug with the other. The group receiving both drugs was increased to 195.

Neither advanced age nor cardiac disease was found to be a contraindication. The drugs not only reduced the burden of nursing care but also opened up possibilities of psycho-

therapy in some patients who had been confined for more than 40 years. 2 references. 2 figures.—*Author's abstract.*

146. *Treatment of the Nonhospitalized, Emotionally Disturbed Elderly Person.* EWALD W. BUSSE, Durham, N. C. Geriatrics *11*:173–179, April, 1956.

The stresses of advancing age result in an increase in the frequency and severity of emotional disturbances in older persons. Hospitalization of these patients is often believed the treatment of choice but, in reality, if the patients are properly handled in their home, they will respond promptly in a most gratifying manner. This paper is based in part on evidence obtained by the interdisciplinary, gerontologic research team at Duke University. This team of representatives from the fields of anatomy, anthropology, medicine, psychology, and social work worked with the normal, well-adjusted older person as well as with the disturbed patient. From these studies it is evident that certain reactions increase in frequency with old age. These include depression, hypochondriasis, irritability, hostility, and an apparently purposeless wandering. The dynamics of depressive episodes in older persons is often different from that found in younger subjects. Depression in older persons is more often traceable to loss of self-esteem due to an inability to feel worth while and expend energy, rather than as in younger subjects, the turning inward of hostile feelings. The best defense against depression for the retired person is participation in recreational activity that has a strong creative element in it. It is important for the older person to feel he is accomplishing something and is admired for it. Hypochondriasis is often used as a way to explain in a socially acceptable way an inability to continue to achieve. The chronic complainer of advanced years is attempting to fill an emotional need that is definitely lacking. Most of these patients have a poor relationship with their children, and many of them have been self-centered in their past life. Treatment must be aimed at first fulfilling their need and then shifting their interest away from themselves. The older person often feels threatened and retaliates with aggressiveness and hostility. It is desirable that those things that are most apt to threaten an older person be recognized and that the patient's feelings not be increased by pointing them out to him or making him recognize them. Wandering is an attempt to replace the lost things in the older person's life and, if he can be given a significant role in his environment and be provided with new experiences, the irresponsible wandering will cease. 6 references. 3 tables.—*Author's abstract.*

PSYCHIATRY OF CHILDHOOD

147. *The Adolescent in the Psychiatric Hospital* (*L'Adolescent à l'Hôpital Psychiatrique*). P. SIVADON, M. SCHWEICH AND A. HAIM, Hyg. ment. *44*:81–95, 1955.

This article reviews the experience of the authors with a group of adolescent subjects in The Center of Treatment and Social Readaptation at Neuilly sur Marne (France) during 1954 and 1955. It should be noted that this center is one of the most progressive in France.

The group consisted of 24 young men between the ages of 17 and 21. In group 1 were 13 schizophrenic persons and in group 2 were 11 neurotic persons with symptoms of depression, social inadaptability, or character disorders. The first step consisted in bringing the group to-

gether in a single building for treatment. This favored blossoming of the classical adolescent crisis of opposition and search for originality (Debesse). When it occurred, it was considered a sign of progress, which the psychiatrist in charge condoned. This regrouping of adolescent subjects with varied symptomatology caused a remission in 4 schizophrenic subjects who joined the active neurotic persons of group 2. The reaction of adult patients toward adolescent patients was either that of aggressive rejection or of indulgent acceptance. Both attitudes covered feelings of jealousy. The reaction of the personnel paralleled the ambivalent attitude of society in general toward adolescent persons. The personnel favored regressive activities, such as participation in menial ward work, and resented expressions of self-assertiveness and rebellion so necessary to the reorganization of sick adolescent patients. The patients' reaction toward work will be studied separately in another paper.

At the end of a year of study all the neurotic adolescent patients of group 2 left the hospital. Some went back to their vagrant life, but the majority reorganized themselves on a high social level by going back to school or by learning a trade. The exact statistics are not made available in the paper.

The authors conclude that in their experience the formation of a group of adolescent subjects in adult inpatient service has definite beneficial results.

PSYCHIATRY AND GENERAL MEDICINE

148. *Occupational Stress and Emotional Illness.* JACKSON A. SMITH, Omaha, Neb. J. A. M. A. *161*:1038–1040, July 14, 1956.

Ninety-one patients, whose difficulties were attributed directly to their occupations, were seen for psychiatric consultation for four years. It was found, however, that in 49 patients the symptoms resulted from an interpersonal conflict with another employee, most frequently the immediate supervisor. An anxiety reaction developed in 18 patients following the illness of another employee who was doing the same kind of work, the cause of the illness frequently being attributed to the occupation. A pre-existing tension state that was actually unrelated to the job was noted in 8 patients. In only 7 did the job itself appear to be the cause of the illness. These 7 patients had been engineers on steam locomotives for an average of 13 years and were unable to gain confidence in themselves operating diesel locomotives; consequently they became anxious, indecisive, and fearful. Nine patients had symptoms typical of conversion hysteria. None of these 91 patients related their interpersonal conflicts to their symptomatology, and in none did a somatic illness secondary to the prolonged tension state develop.—*Author's abstract.*

149. *Consequences of Anxiety: The Emotions and the Heart.* EDWARD WEISS, Philadelphia, Pa. Geriatrics *11*:151–158, April, 1956.

One of the most important and most difficult subjects in clinical medicine is the problem of anxiety and the heart. An anxious person with a normal heart can often be reassured and told to go about his business. An anxious person with a diseased heart cannot, but when he is told to rest and is given other precautions he often becomes an invalid, more from the fear of disease of the heart than from the disease itself. This poses a very difficult question

because the problems of psychosomatic relationships in cardiovascular disease may be very complicated and may depend as much upon an analysis of personality as upon an evaluation of cardiovascular disease.

Any pain from nose to navel must be taken seriously and the various necessary physical studies must be done. Then if physical disease can be excluded safely, the question of reassurance arises. Reassurance alone may need to be repeated constantly, and one must try to understand the background of the anxiety so that symptom formation may not be necessary.

So often after myocardial infarction the heart heals but the patient remains an invalid for anxiety reasons. Here a personality study will permit the physician to judge whether the patient is one who accepts dependency, thinks in terms of retirement, and becomes an invalid (perhaps subsisting on insurance benefits), or whether he will fight against dependency, perhaps erring in the other direction by refusing suggestions and indulging in rash behavior. It may be necessary to deal with persons who have guilt and hostile feelings. It also should not be forgotten that the age when coronary disease occurs is also the period of diminishing potency and that many sexual problems arise that are capable of causing great tension. These, too, have to be considered in relation to coronary circulation. Finally, depression is often masked by heart symptoms that must be recognized and dealt with appropriately.—*Author's abstract.*

For Reference

150. *An Outline for a Curriculum for Teaching Psychiatry in Medical Schools.* COMMITTEE ON MEDICAL EDUCATION, AMERICAN PSYCHIATRIC ASSOCIATION. J. M. Educ. *31*:115–128, Feb., 1956.

PSYCHIATRIC NURSING, SOCIAL WORK, AND MENTAL HYGIENE

151. *Time Is the Essence—of What?* NANDOR FODOR, New York, N. Y. Internat. Rec. Med. & G.P.C. *169*:526–538, Aug., 1956.

An attempt is made in this study to correlate semantic concepts of time, through personification, objectification, and geometrization, with psychologic reactions in waking and in dream life. The struggle for overcoming time or succumbing to it and the dynamic concepts and subjective evaluation of time, together with calendric dreams, problems of duration, and varieties of temporal neuroses are discussed with illustrations from clinical experience. 11 references.—*Author's abstract.*

PSYCHOANALYSIS

For Reference

152. *Dreams, Images, and Perception: A Study of Unconscious-Preconscious Relationships.* CHARLES FISHER, New York, N. Y. J. Am. Psychoanal. Assoc. *4*:5–48, Jan., 1956.

153. *Phrenology Versus Psychoanalysis.* KARL M. DALLENBACH. Am. J. Psychol. *68*:511–525, Dec., 1955.

PSYCHOPATHOLOGY

154. *Some Comments on the Nature, Diagnosis and Prognosis of Neurotic Anxiety.* DAVID P. AUSUBEL, Champaign, Ill. Psychiatric Quart. *30*:77–88, Jan., 1956.

Anxiety is conceptualized as a specific kind of fear response or tendency to respond with fear to anticipated situations that are perceived as threats to an individual's self-esteem. It differs from ordinary fear in that the source of the threat is referable to the future rather than to the present. Anxiety differs from feelings of insecurity, which also arise in response to anticipated threat, in that the threat is specifically directed against the individual's self-esteem and not against his physical safety. In many situations, however, insecurity and anxiety are aroused concomitantly. The concept of objectless fear is psychologically meaningless. In cases of supposedly free-floating anxiety, careful examination invariably reveals that an actual threat is operative, even if it cannot always be identified by the patient. Furthermore, in many undoubted cases of clinical anxiety, patients enjoy relatively complete and precise insight into the objects of their dread.

The characteristic feature of neurotic anxiety is a tendency to overrespond to threats directed against self-esteem, particularly to those posed by novel adjustive situations. But in terms of the essential or predisposing cause of neurotic anxiety, an existing state of catastrophically impaired self-esteem, the response is not disproportionate to the degree of subjectively experienced threat.

It is postulated that neurotic anxiety only occurs in persons who, as a result of not being accepted and intrinsically valued as children, do not enjoy an intrinsic sense of adequacy that is independent of their performance ability and success in life. Such persons are vulnerable to neurotic anxiety because their self-esteem is wholly a function of the realization of their compensatorily exalted and highly tenacious ambitions.

The prognosis for complete cure of neurotic anxiety is regarded with pessimism, but several effective steps can be taken to prevent acute exacerbations of anxiety. In the stage of panic, drastic measures are indicated (anything that will reduce anxiety quickly and effectively), such as the use of reserpine and mephenesine, reduction of the burden of immediate pressures and demands on the patient and rendering of supportive and paternalistic therapy. At this point the patient is incapable of taking any action or making any rational decision. He has to be told what to do if he is to receive the benefit of any help.

Accurate diagnoses of neurotic anxiety can only be made by specially empathic clinicians who have adequate theoretic and clinical training. The fact that projective tests require special skills of a subjective nature in order to be valid does not in any sense destroy their clinical usefulness. 2 references.—*Author's abstract.*

TREATMENT

a. General Psychiatric Therapy

155. *Experiments with Music in a Mental Hospital.* A. ZANKER AND M. M. GLATT, Warlingham, Surrey, England. Monatschr. f. Psychiat. u. Neurol. *131*:215–225, April, 1956.

Experiments were done to study reactions of two groups of patients, neurotic subjects

and alcoholic subjects, to music. Twice weekly recitals were given by distinguished musicians, followed immediately by a discussion of the patients' reactions. Use was made also of two questionnaires to evaluate the influence of music on the groups in general and to analyze the reactions of individuals to the musical items.

Discussions following the recitals showed that there was more readiness to talk among the group of alcoholic persons; more reluctance to do so and more inhibition was noted among the neurotic subjects. These results correspond to the greater inclination to act out among alcoholic subjects (particularly among the psychopathic type of alcoholic), the generally more reserved neurotic persons being more inclined to erect and maintain defences.

The patient's personality and general attitude or mood at the time of the recital were important factors in determining the general reaction to the whole recital. Thus positive (sometimes enthusiastic) responses usually mirrored a positive attitude of the patient to the hospital, the staff, and to treatment in general; negative responses frequently coincided with a negativistic attitude toward the hospital and toward treatment, whereas responses denoting indifference were often given by rather apathetic patients lacking interest and initiative.

In general it was found that patients' reactions may sometimes be of diagnostic value by revealing unconscious attitudes. In therapy music may serve as an adjunct to psychotherapy by fostering abreaction and, by breaking down defences, it may provide material for interpretation.

As far as individual reactions are concerned, of particular interest was the finding that the patients' responses often showed marked incongruity in relation to the intricate character of the musical item; for example, reactions of bleakness and distortion to an intrinsically harmonious and joyful musical piece were noted. It was believed that the reason for such incongruity of response was frequently the tendency of the subjects to project their own attitudes and moods into the music. Analysis of such incongruous responses often helped to shed light on the subject's unconscious attitudes and conflicts. While incongruity of response therefore appears to be of diagnostic value, such subjectivity of a person's responses, with other variable factors, makes objective research in the field of music therapy difficult. 9 references.—*Author's abstract.*

b. Drug Therapies

156. *The Use and Abuse of Sedative and Hypnotic Drugs.* FRANKLIN G. EBAUGH, Denver, Colo. Postgrad. Med. *19*:513–525, June, 1956.

In general sedatives counteract overstimulation without producing sleep or drowsiness, whereas hypnotics are used for the production of sleep. A newer group of drugs, the ataraxics, are discussed briefly. These drugs have a tremendous value in relieving discomfort and at times preserve life; however, they should be prescribed with knowledge of the best utility as well as with an awareness of the dangers. Indications for short-term usage are listed. The single indication for prolonged usage of these drugs relates to their anticonvulsive properties. Frequently, sedatives are prescribed as a crutch, leading to psychologic and physiologic dependence, and their usage may prevent the patient from seeking definite psychiatric treatment. Too often it is easier for the physician to continue having the

patient use these drugs than to direct him more specifically to his problems. Attention should be paid to the site of detoxification and to the route of elimination of the drugs, and they should be given with caution to persons who have severe liver or kidney impairment.

One of the most important tools in dealing with patients with disturbed feelings and emotions is the physician-patient relationship. This is of great importance, not only to the psychiatrist but to all physicians. Physiologic dependency may become a real problem, and some observers have considered this a form of addiction. In problems of addiction and habituation there is an interrelationship of the preaddiction personality, that of the relief of tension and heightened self-esteem achieved by the drug, with ultimate social and personality disorganization. The physician can do much to determine the attitude of the patient in discouraging psychic dependency that might lead unwary persons to habituation or addiction. Signs of intoxication and addiction are listed, and treatment is discussed. 21 references. 8 tables.—*Author's abstract.*

157. *Reserpine; Alone and as an Adjunct to Psychotherapy in the Treatment of Schizophrenia.* RICHARD C. COWDEN, MELVIN ZAX, AND J. A. SPROLES, Gulfport, Miss. A.M.A. Arch. Neurol. & Psychiat. *74*:518–522, November, 1955.

The most exacting test of the effectiveness of the drug reserpine would be in using it with chronic, severely disturbed and agitated patients who had failed to improve under the usual regimen of treatment, such as insulin coma and electroconvulsive therapy. Thirty-two chronic, severely disturbed schizophrenic patients in the maximum security ward were selected for the experiment. They were assigned to one of four groups of 8 patients. Group A received group psychotherapy and reserpine; Group B received group psychotherapy and a placebo; Group C received only reserpine; Group D served as the control group. Medication was continued for six months; maximum dosage was 8 mg./day; the average dose was 4 mg./day. No remarkable side effects were noted. Psychotherapy sessions were held three times per week, one hour per session. The methods used to obtain change varied from being very directive and at times punitive to being completely accepting and nondirective. The measurements of improvement were purely behavioral ones, only one of which required any subjective clinical judgment.

The results show that dramatic changes took place in the behavior of all three treatment groups. None of the treatments was effective in changing the schizophrenic process itself, only the manifestation of the illness. The group receiving both reserpine and psychotherapy showed the greatest over-all improvement. In all the treatment groups, the greatest change occurred with those patients who showed the highest level of manifest anxiety, agitation, and a tendency to "act out" their impulses. Theoretically the results suggest that there are different types of patients based on a physiologic or biochemical criterion rather than the present symptomatic nosology. 5 references. 2 tables.—*Author's abstract.*

158. *Alteration of Copper Metabolism in Chlorpromazine-Treated Cases.* H. AZIMA AND A. RICHMAN, Montreal, Canada. A.M.A. Arch. Neurol. & Psychiat. *75*:163–166, Feb., 1956.

The combination of extrapyramidal signs and liver damage in patients treated with

chlorpromazine led to the supposition that perhaps the phenomena represented a hepatolenticular disturbance similar to Wilson's disease. Since in Wilson's disease the metabolism of copper is altered, a study was undertaken to investigate whether there was an alteration of copper metabolism in patients receiving chlorpromazine.

The plasma copper level of 25 psychiatric patients was measured before and at the end of the first, third, and fifth weeks after treatment with chlorpromazine. Urinary amino acids were investigated in patients who showed extrapyramidal signs. Liver function tests were performed in all patients at weekly intervals. A control group consisted of 25 psychiatric patients who received other forms of treatment, e.g., insulin coma, electroshock, reserpine, or other therapies.

The majority of the patients treated with chlorpromazine showed a gradual rise in the plasma copper level, in 12 of whom it was definitely abnormal. Of these 12 patients, 5 manifested extrapyramidal signs, and in 2 these signs were quite marked. In no case was there a combination of plasma copper rise, liver damage, and extrapyramidal signs. No patient manifested extrapyramidal signs without a rise in plasma copper. Urinary amino acids were within normal limits in all patients showing neurologic signs.

The data demonstrate that chlorpromazine provokes an alteration of copper metabolism in the body. Because the indirect-reacting fraction of plasma copper was not investigated in the present series, we are not justified in concluding that there is an identity between the changes produced by chlorpromazine and those produced by Wilson's disease. However, because of the similarity of the clinical picture of chlorpromazine complications (hepatic and lenticular) to that of Wilson's disease, this theory cannot be excluded. 15 references. 2 figures.—*Author's abstract.*

159. *Medico-Psychological Viewpoints on Narco- and Hypno-Analysis.* B. STOKVIS, Leyden-Oegstgeest, The Netherlands. Monatschr. f. Psychiat. u. Neurol. *131*:247–251, 1956.

The objectives of narcoanalysis are to extend and supplement available anamnestic data, to facilitate abreaction of affect-laden experiences, and to obtain from the person under treatment any data of medicoforensic importance. The author prefers hypnosis to narcoanalysis because the state of lowered consciousness is more easily regulated, because, when the patient has been awakened from the hypnotic state, he is usually quite clear mentally, and because by applying hypnosis undesirable side effects can be avoided. In the presence of pregenital conflicts both narcoanalysis and hypnoanalysis should be strictly avoided. After describing his technique, the author stresses that hypnocatharsis is only admissible in those cases in which a recognizable, well-defined conflict exists. In conclusion the author refers to some drawbacks inherent in hypnocatharsis and narcoanalysis. 2 references.—*Author's abstract.*

c. Psychotherapy

160. *Psychotherapy and the Ministry.* ABRAHAM N. FRANZBLAU, New York, N. Y. Internat. Rec. Med. & G. P. C. *168*:793–797, December, 1955.

It is important that boundaries be marked between the roles of minister and psychiatrist

in dealing with human troubles and conflicts. The minister offers advice, rebuke and correction, solace and comfort, specific help in crises, a listening ear, perspective in seeing a problem in its larger contexts, restoration of objectivity and judgment, and the efficacy resident in prayer. Beyond this, trespassing the boundaries of psychiatry may occur.

The minister has, by definition almost, certain hampering limitations in approaching the psychiatric function: he cannot be nonjudgmental because he is publicly committed to a moral code; he cannot hold one set of values in the therapy room and another in the pulpit; he is committed to his whole congregation and to a multiplicity of roles, and he cannot limit his field of operation. He cannot isolate himself, as a psychiatrist can, from family and friends, nor can he as readily handle infatuations and hostilities generated by the therapeutic situation or countertransferences. He has much less control over the therapeutic situation than the psychiatrist, which makes it, in his hands, much less amenable to scientific discipline; he operates under the stimulus of the person's need and is permitted to help directly, while the therapist must have a diagnosis and must frustrate the call for help to eliminate the patient's dependency. The minister is apt to respond with superficial and perhaps even harmful reactions if he does not understand the dynamics of the situations that are presented, for example, to attempt to cheer a person in a depression, to be permissive with a person who tends to act out, to give simple reassurances to a phobic person, to rebuke and punish a masochist, or to pander to dependency. Failure to understand unconscious sexual attractions can also be a source of great difficulty. Punitive attitudes with the wrong person may push him into suicide. Without proper training, such situations may lead to tragedy.

Psychiatrists are licensed physicians, given by law the right to make diagnoses, prescribe and administer treatment, but also charged with responsibility for malpractice. If the minister wishes to practice psychiatry, he must first obtain the necessary training; his training in theology does not qualify him, no matter how ardently he wishes to help people. The fact that the need exceeds the supply of therapists does not justify entrance of nonqualified personnel into the field. Under psychiatric supervision, however, ministers may make a genuine contribution in an institutional context, even in the role of therapists.—*Author's abstract.*

d. The "Shock" Therapies

161. *Evaluative Study of One Hundred Transorbital Leucotomies.* MATTHEW D. MERMELSTEIN, Clarinda, Iowa. J. Clin. Psychol. *12*:271–276, July, 1956.

This paper reports the results of a program carried out at the Clarinda, Iowa Mental Health Institute from November, 1951, to July, 1953, involving 104 operations during which Fiamberti's transorbital leukotomy was performed. The method consisted of first anesthetizing a patient with one or two electric shocks, then inserting a Steinmann pin beneath the upper eyelid and driving it through to the anterior part of the frontal lobe. Medial, lateral, and vertical incisions were made. The 104 transorbital leukotomies were performed on 102 patients, and two were repeated. Two patients died as a result of the operation. The evaluation is, therefore, based on a total of 100 patients.

The largest number of cases (67 per cent) were in schizophrenic persons and the largest number of these (29 per cent) were in patients with long-term chronic diseases. However, improvement did not seem to depend upon length of hospitalization, as shown by the fact that in the one to two year group 17 per cent gave over-all positive results, whereas the three to five year group showed a 30 per cent gain, the six to ten year group showed a 27 per cent gain, and the 11 year group showed a 20 per cent gain. It was concluded that the amount of improvement could be best described as due to some fortuitous circumstance associated with the operation and subsequent hospital care.

A comparison of the short and long-term ratings of the improvement of the patients indicated a relapse rate of 41 per cent. One and a half to three years later it was found that 75 per cent showed no improvement, 14 per cent showed at least some slight improvement, and 9 per cent showed moderate to good improvement. Reduction of violent behavior, tension, and anxiety was not substantially accomplished. Over two thirds of the most combative and most disturbed patients showed no appreciable gain one and a half to three years later, and it was necessary to place them on maximum security wards where additional restraint, symptomatic electric shock, and sedation were required. In 6 per cent of the cases epileptiform seizures developed which had not been previously manifested. Work output of those operated upon increased. Twenty-two per cent showed a greater tolerance in assuming more responsibilities, thus increasing the supply of patients who were hospital workers. Of the 102 patients who underwent surgery, 12 left the hospital. Six suffered relapses and returned, 5 are still on convalescent leave status, and 1 has been discharged as cured. Seizures developed in the latter patient and she continued to receive anticonvulsive medication after leaving the hospital.

Evaluation proved extremely difficult due to the fact that leukotomy apparently causes both gains and losses in behavior and requires nursing care and supervision. 3 references. 2 tables.—*Author's abstract.*

162. *Lobotomy: A 6-Year Follow-up of 45 Patients.* MARVIN J. SCHWARZ, Chicago, Ill. Am. J. Psychiat. *113*:224–227, Sept., 1956.

Forty-five patients were followed for an average of six years following lobotomy. In 38 of these schizophrenia was preoperatively diagnosed. Miscellaneous diagnoses were made in the remainder. The patients did not appear to be essentially improved six years postoperatively. Large numbers were still in disturbed wards, and only 13 had been discharged. The results in this series were poor as compared with most other reports in the literature. The patients who remained in the hospital especially did not do well. It is suggested that much of the difference in results between studies may lie in differences in methodology and of patient evaluation, with related differences in criteria for definition of improvement or lack of improvement. These patients represented administrative, therapeutic, and behavior problems to the hospital before and after surgery, as they did six years later. 16 references. 5 tables.—*Author's abstract.*

neurology

CLINICAL NEUROLOGY

163. *Fatalities in Myasthenia Gravis: A Review of 39 Cases with 26 Autopsies.* LEWIS P. ROWLAND, PAUL F. A. HOEFER, HENRY ARANOW, JR., AND H. HOUSTON MERRITT, New York, N. Y. Neurology *6*:307–326, May, 1956.

Among 180 patients with myasthenia gravis was a known fatality rate of at least 30 per cent. The records of 39 of these patients who died were reviewed in an effort to evaluate factors that might be responsible for death and to describe the clinical and pathologic features of a group of patients in whom the disease has been followed to its end.

In more than half of the cases terminating fatally, the patient died within two years of the onset of symptoms and the mean duration was 2.8 years, ranging from 2 weeks to 12 years. Fulminating cases were observed in both sexes and in older patients as well as in young persons. Although the nature and severity of symptoms varied from patient to patient, in all but 1 of the cases terminating fatally did the patient show evidence of generalized myasthenia prior to death.

Complicating major illnesses occurred in 12 patients, but in all of them muscle weakness played a prominent role in the circumstances preceding death. Two deaths were associated with thyrotoxicosis and 2 with pregnancy; the effects of these conditions on the myasthenic state were noted to be unpredictable. Respiratory infections preceded the terminal crises in 10 patients, but no overt precipitating illness occurred in 17 patients.

Thirteen patients died suddenly and unexpectedly during episodes of respiratory distress which lasted from a few minutes to one hour. Although respiratory paralysis seemed to be most frequently responsible, obstruction due to lingual, glottal, or laryngeal paralysis was suspected in some patients, and reflex cardiac arrest may have occurred in others. Several patients had acute episodes of dyspnea which were relieved by neostigmine prior to the final attack, and it is suggested that these attacks should be recognized as premonitory; the maintenance dose of neostigmine (or other therapeutic agents) should be increased and all precautions taken.

Sixteen patients were in a mechanical respirator at the time of death. All but 2 suffered anoxic insult prior to the institution of respiratory therapy, and, among those examined at autopsy, pulmonary disease was universal. The importance of instituting artificial respiration early, of maintaining a patent airway, and of improving methods for the prevention of pulmonary complications is stressed.

Several patients showed little or no response to large amounts of neostigmine in the terminal phases, and drug refractoriness was thought to be an important consideration in some seriously ill patients. No definite instances of weakness due to overdosage of medication occurred in this series, but cessation of drug therapy or reduction of dosage has been practiced and is recommended for patients in a mechanical respirator. For patients with

ventilatory insufficiency who are not in a respirator, the use of barbiturates, opiates, and placebos may be dangerous.

The most important pathologic changes occurred in the thymus, heart, and skeletal muscle. Thymomas were present in 9 of 26 patients subjected to autopsy, but no thymic tissue was found in 8 patients. The presence of germinal centers in non-neoplastic thymic tissue was not as prominent in this series as it has been in others. Myasthenia did not develop in 2 patients until after the removal of a thymoma, and in 1 patient there was roentgenologic evidence of a tumor for 20 years, although he was free of symptoms most of the time. These findings raise questions as to the relationship between myasthenia gravis and thymic abnormalities.

Lymphorrhages occurred in the muscles of 15 patients. Actual necrosis of muscle fibers with an inflammatory cellular reaction was found in the skeletal muscles of 3 patients, and 3 patients also had myocarditis. These changes may be an integral part of the disease, and any theory of the pathogenesis of myasthenia gravis should take them into account. 4 figures. 5 tables.—*Author's abstract.*

164. *Cerebral Arteriosclerosis: Anatomico-clinical and Statistical Study* (*Artériosclérose cérébrale; étude anatomo-clinique et statistique*). JACQUES BOTTON. Encéphale *44*:350–396, 1955.

In a study of cerebral arteriosclerosis in 862 neuropsychiatric patients, whose average age was 68.9 years, it was found that there were no definite criteria by which the diagnosis of cerebral arteriosclerosis could be made. While the incidence of cerebral arteriosclerosis increases with age, it is not to be considered as simply a manifestation of old age. A particular type of cerebral arteriosclerosis, scalariform arteriosclerosis, is often associated with generalized arteriosclerosis and hypertension in relatively young persons; this is the form often designated as "malignant arteriosclerosis" and is more frequently associated with neurologic "accidents" than other types. It was found in this series that cerebral arteriosclerosis almost always begins in the arteries at the base of the brain, especially in those arteries derived from the internal carotid artery and the middle cerebral artery. No correlation was found between the occurrence of cerebral arteriosclerosis and anomalies of the circle of Willis. While hypertension and hypercholesteremia were found to be present in most cases and often proportional to the severity of the cerebral arteriosclerosis, yet they were not found to be indispensable to the development of the arteriosclerosis, and their mode of action is still not well understood. While syphilis, alcoholism, dementia praecox, and paranoid dementia were rarely associated with cerebral arteriosclerosis in this series of cases, diabetes, senile dementia, and hyperostosis frontalis interna were often associated. 80 references. 6 figures. 10 tables.

165. *Myasthenia Gravis: A Personal Study of 60 Cases.* HUGH GARLAND AND A. N. G. CLARK, Leeds, England. Brit. M. J. *1*:1259–1262, June 2, 1956.

A series of 60 patients seen in 15 (interrupted) years is reviewed. In relation to the total population from which these patients are likely to have come, the incidence in this part of Great Britain is at least 1 in 40,000 of the population, so that there are probably at least 2000 examples at any one time. Seven of 60 patients were untraceable. There were 35 women

and 25 men, and the age at onset of presenting symptoms ranged from 6 to 75 years; in 40, symptoms first appeared between the ages of 21 and 50 years, but in 3 the first symptoms appeared after age 65. The shortest duration of symptoms in a case in which the patient died was one year and the longest history of continuing symptoms 28 years. The duration of the illness before a diagnosis was established varied from one week to 20 years. Ocular symptoms occurred in 90 per cent and bulbar symptoms in 36 per cent. Twelve patients had complained only of ocular symptoms at the time of writing, and only 5 of the 53 had never complained of ocular symptoms. The diagnosis is often overlooked in the early stages especially when there is a monosymptomatic onset. In 50 per cent of patients no complete remission had occurred at the time of writing.

The discovery of neostigmine has revolutionized prognosis and treatment. Four patients in the series had taken as much as 1000 mg. a day for long periods, and one had taken 600 mg. a day for 20 years. Personal experience with more modern drugs, with radiation to the thymus, and with thymectomy was not sufficiently extensive to be of significance, although the 6 persons subjected to thymectomy seemed to show no benefit. The mortality in the medically treated cases still was about 20 per cent. This figure could probably be lowered if all patients were immediately admitted to the hospital when dyspnea appeared; they could now be kept alive by modern methods of artificial respiration. 18 references. 3 tables.—*Author's abstract.*

166. *Relaxant Effects of Meprobamate in Disabilities Resulting from Musculoskeletal and Central Nervous System Disorders—Clinical Observation of Fifty-Five Cases.* HARRIET E. GILLETTE, Atlanta, Ga. Internat. Rec. Med. & G.P.C. *169*:453–468, July, 1956.

Meprobamate was used as an adjunct to the psychiatric management of 55 patients for periods up to six months. Twenty-seven had musculoskeletal disabilities and 28 were suffering from neuromuscular disturbances resulting from pre- or paranatal damage to the central nervous system.

Initially, 800 mg. three times a day were recommended for adults. Later the dose was adjusted if advisable to 400 mg. on the same schedule. Children less than 10 years of age usually received 200 mg. three times a day. However, 1 child with severe tension athetosis became drowsy on this dosage. Daytime somnolence was eliminated without interfering with the relaxant effects of the drug by administering a single dose of 800 mg. at bedtime.

In patients with musculoskeletal disorders, 1.2 Gm. daily sufficed for 76 per cent; 12 per cent required a total daily dose of 2.4 Gm.; and 12 per cent received 1.6 Gm./day. Of the patients with central nervous system lesions, 23 per cent required a total daily dose of 2.4 Gm.; for 53 per cent 1.2 Gm./day was sufficient. The other patients received smaller total daily doses in most instances.

Musculoskeletal disorders treated in the early, acute stages responded most satisfactorily. In 40 per cent of this group, pain, spasm, and emotional tension were completely relieved and range of motion was restored as nearly as possible to normal (4+ result). In an additional 54 per cent, improvement was definitely increased over the response to physical therapy alone (3+ or 2+ result). The progress of all patients in this group was more satisfactory after meprobamate was added to the regimen, and physical therapy could be

terminated earlier. Meprobamate is now used in this clinic almost routinely as a supplement to physiatric treatment of whiplash injuries, the shoulder-hand syndrome, and acute low back disabilities.

Some degree of improvement was discernible in 76 per cent of the patients in the group with central nervous system lesions after addition of meprobamate to physical therapy. Those with cerebral palsy showed presumptive evidence of a regulatory effect on the central nervous mechanism, which was somewhat more pronounced in the patients in the group with tension athetosis. Perceptible muscular relaxation with lessening of flailing movements occurred in most subjects, so that braces could be more readily applied and the patients more easily handled. In spasticity caused by cerebral damage, muscular relaxation was more limited.

The first signs of clinical response were detectable in a few hours, and the peak of effect was reached in four days or less. Relaxation continued throughout the period of treatment. Rarely was it necessary to increase the dose to support the initial results. All chronic patients who improved on supplementary medication relapsed on cessation of the drug, usually in about two days. Generally there was a distinct improvement in disposition and, in the children, a tendency to gain weight.

Meprobamate appears to alter the neuromuscular mechanisms as well as to lessen psychic tension. Thus muscle tonus is reduced, and spasm and rigidity are released to a degree over and beyond the effect achieved by relief of emotional stress alone. 28 references. 2 tables. —*Author's abstract.*

167. *Electrophysiologic and Clinical Observations in Hemifacial Spasms.* ANDRE A. WEIL AND WILLIAM A. NOSIK, Cleveland, Ohio. Neurology *6*:381–389, June, 1956.

Hemifacial spasms occur in a variety of neurologic disorders, usually accompanied by additional neurologic signs and symptoms of systemic or regional origin. Hemifacial spasms occurring as isolated neurologic or psychoneurologic phenomena can be classified by simple clinical and electrophysiologic observations into (1) hemifacial spasms due to cortical irritation, (2) involvement of the facial nucleus or nerve radix, and (3) psychogenic conversion reactions (habit spasms). Hemifacial spasms due to cortical irritation are uncommon; they are accompanied by repetitive and single spike firing from various mimetic muscles and also by focal disturbances of cerebroneuronal rhythmicity in the electroencephalogram. Hemifacial spasms of nuclear or radicular origin can be subclassified as cryptogenic facial spasm (infectious, degenerative, inferior anlage), "reaction a distance" (lesions of peripheral branches of the facial nerve), and postparalytic (following Bell's palsy). All show characteristic electromyographic patterns but no definite electroencephalographic disturbances of cerebral rhythmicity. The site of greatest clinical disturbance does not always correspond with the site of maximal fasciculatory spike firing. This bears a relationship to the selective partial neurectomy of the facial nerve as the neurosurgical treatment of choice. Hemifacial spasms due to psychogenic conversion reactions are twice as common as are hemifacial spasms of organic etiology. They affect one or both sides of the face and can be temporarily abolished by intravenous amobarbital sodium injections. Electromyographic recordings show muscle contraction bursts identical to the ones seen in voluntary movements. 22 references. 7 figures.—*Author's abstract.*

CONVULSIVE DISORDERS

168. *Vestibular Epilepsy.* SIMON BEHRMAN, London, England. Brain *78*:471–486, 1955.

On recovery of consciousness following an epileptic seizure, a few persons for a variable period experience vertigo, which is occasionally associated with tinnitus. This postictal vertigo may be disabling, making locomotion impossible for from a few minutes to an hour. As a rule similar vertiginous sensations, often provoked by quick movements, are also experienced between seizures.

Unlike preictal vertigo, postictal vertigo is a rare clinical phenomenon. This was confirmed by questioning a large control group of epileptic subjects. Furthermore, a study of the case histories did not reveal that cerebral lesions giving rise to epilepsy with vertiginous aura are associated with postictal vertigo. These negative points suggest that postictal vertigo is not an integral part of the epileptic phenomenon. On the other hand, the constant association between postictal and interictal vertigo already mentioned points to a common underlying mechanism. The occasional linkage with tinnitus or deafness, and with the ready provocation of vertigo by movements of the head and other clinical features revealed by analysis of a number of these case histories, suggests that the interictal vertigo has a vestibular origin. Bearing in mind, then, the common mode of origin of interictal and postictal vertigo, it must be assumed that both these forms of vertigo are engendered by activation of the vestibular apparatus. This conclusion is further supported by those case histories that, in addition to interictal and postictal vertigo, also show clear evidence of vertigo immediately before the commencement of seizures.

If the vestibular origin of pre- and postictal vertigo is accepted, the ictus also can be reasonably regarded as having been precipitated by the vestibular activation, and vestibular epilepsy is the suggested designation for this entity. The epileptic nature of the attacks is indicated by loss of consciousness, often protracted, in the absence of obvious disturbed circulation and the occurrence of convulsions in some cases.

The clinical classification of vestibular epilepsy is suggested and the differential diagnosis is discussed, as are other conditions in which disturbances of vestibular apparatus are associated with unconsciousness. Arguments are advanced suggesting that vestibular epilepsy is a subgroup of sensorily precipitated epilepsy, namely, epilepsy provoked under certain circumstances in constitutionally predisposed persons by stimulation of various types of receptors. 29 references.—*Author's abstract.*

169. *Comments and Observations on the Nature of Narcolepsy.* ROBERT E. SWITZER AND ARTHUR D. BERMAN, Portsmouth, Va. Ann. Int. Med. *44*:938–957, May, 1956.

This paper developed from the authors having questioned a long-standing and classic concept of idiopathic narcolepsy. In the beginning of the paper a rather detailed history of a 20 year old man who had had all the components of the narcolepsy syndrome is included to consider the nature of narcolepsy. Then follows a historical resume of a symptom complex and a brief presentation and discussion of the various theories of the origin of both symptomatic and so-called idiopathic narcolepsy. A review of the literature, as understood by the authors, seems to indicate that idiopathic narcolepsy is a functional illness, not beyond under-

standing and not lacking in demonstrable psychopathology. The authors then present in detail their study and treatment of the afore-mentioned patient and include their observations from the neurologic, clinicopsychologic, and psychiatric approach in their attempt to verify a belief that a narcolepsy syndrome should never be considered idiopathic in nature unless the diagnosis is arrived at by the inclusion of a search for psychogenic causes in the study of the patient. 51 references.—*Author's abstract.*

170. *Mescaline and LSD-25 in Activation of Temporal Lobe Epilepsy.* BERT E. SCHWARZ, REGINALD G. BICKFORD, DONALD W. MULDER, AND HOWARD P. ROME, Rochester, Minn. Neurology *6*:275–280, April, 1956.

There is a striking resemblance between the action of mescaline and d-lysergic acid diethylamide (LSD-25) in their widespread psychic effects and to analogous phenomena that occur in the so-called functional psychoses. The affective reactions and the distortion of ideational content seem to be patterned on a frame of reference colored by previous experiences.

John Hughlings Jackson's classic description of the paroxysmal dream state, with associated psychic symptoms of hallucinations, perceptual illusions, affect disturbances, forced thinking, and automatisms occurring in the presence of a relatively clear sensorium, is reminiscent of the manifold effects of LSD-25 and mescaline. For instance, the complex visual and auditory hallucinations, the strange feeling states in which the patient complains of being different or transferred back to some early memory, and the illusions of distortion of size or shape of objects all have been described. The various affect states, such as terror, dread, and euphoria, which are paroxysmal in temporal lobe epileptic persons, occur when mescaline and LSD-25 are employed.

Because of the gross analogy between the phenomena seen in temporal lobe epilepsy and the phenomena seen in the mescaline and LSD-25 psychoses, it seemed valid to inquire into the locus of action of these phenomena by an attempt to trigger seizures by means of drugs. This could be done by using certain drugs that express their effects by way of these channels in much the same way that an exploring electrode can trigger off a temporal lobe focus, producing a stereotyped repetitive picture. Although the electroencephalographic changes occurring after administration of mescaline and LSD-25 are minimal and difficult to interpret, concomitant electroencephalographic tracings were made from 3 patients who had temporal lobe epilepsy.

Judged on the basis of these 3 patients with temporal lobe epilepsy in whom there were good histories of psychic aura, it would appear that mescaline and LSD-25, both powerful hallucinogenic agents, were ineffective as clinical activation agents. It would seem that the action of these drugs in producing experimental psychosis might be a diffuse one, rather than one of selectively activating any single region, such as occurs in temporal lobe epilepsy. Although most of the thoughts of the person with the model psychosis could be explained on experimental factors, it was surprising that virtually nothing was obtained that could be remotely linked with the auras. If the contents of the aura were conditioned by psychic factors, it would seem logical to be able to activate them or at least to produce some related associations with these drugs. Although mescaline and LSD-25 readily released other memories, visions, and the like, they could not precipitate the aura that were physiologically

encapsulated in a damaged area and that were inaccessible to these drug stimuli. However, LSD-25 and mescaline might be useful in distinguishing a psychosis from a temporal epileptic syndrome. The psychosis presumably could be activated, whereas epilepsy would be refractive to these drugs. 9 references. 2 tables.—*Author's abstract.*

171. *Interseizure Disturbances in Focal Epilepsy.* FRANK MORELL, New York, N. Y. Neurology *6*:327–334, May, 1956.

Patients with seizures due to focal cortical lesions frequently show interseizure abnormalities in the form of behavior disorders or mental deterioration. It is also known that these patients show electrographic evidence of a more or less constantly discharging focal abnormality in the electroencephalogram. The possible relationship of this interseizure electrographic abnormality to behavioral changes was investigated by means of establishing conditional responses in which a conditional stimulus, which required the area involved by the discharging focus, was compared with one requiring an uninvolved sensory-receiving area.

In patients with sharply localized temporal lobe spike focuses and with clinical seizures either of the psychomotor type or with an aura suggesting temporal lobe origin, the conditional alpha response to an auditory stimulus was compared with that to a tactile stimulus.

Our results indicated clearly that there was a marked impairment in the ability to form a conditional alpha response to a sound stimulus in patients with temporal lobe lesions. In the same patients the same conditional response could be easily elicited when touch was the conditional stimulus. Thus the discharging temporal lobe lesion selectively impairs the capacity of auditory cortex to participate in new physiologic linkages. Such impairment in the capacity of damaged cortex to participate in the formation of conditioned reflexes may explain much of the interseizure symptomatology of patients with focal epilepsy. 10 references. 2 figures. 1 table.—*Author's abstract.*

172. *Ictal Depression and Anxiety in Temporal Lobe Disorders.* ANDRE A. WEIL, Cleveland, Ohio. Am. J. Psychiat. *113*:149–157, Aug., 1956.

Ictal depressions and anxiety may occur as signs of abnormal rhinencephalia and/or temporal lobe activity, and this activity is usually epileptiform. Ictal depressions lasting from hours to weeks occurred in 7 subjects in whom the principal seizure manifestations consisted of uncinate attacks and temporal lobe automatisms. Depressive episodes preceded or followed temporal lobe seizures or occurred paroxysmally during the free interval. There was electroencephalographic confirmation that this particular type of depressive reaction might be a result of subclinical hippocampal-amygdaloid-temporal lobe epilepsy and/or due to after-discharges from the same structures following manifest seizure activation. The theory is proposed that the limbic system of the brain, which is much concerned with the experience and elaboration of emotions, may be blocked in its experience pattern by certain epileptic discharges. This blocking promulgated expressions in patients such as "feelings of emptiness," "feelings don't reach me any more," and the like, which may be subjectively translated as feelings of depression.

Paroxysmal anxiety was observed in 4 subjects immediately preceding temporal lobe seizures, as well as in the so-called free interval between seizures as an isolated affective

phenomenon. These anxiety attacks seem to bear a relationship to the firing of the temporal lobe cortex as confirmed by electrographic and neurosurgical observations. 23 references. 7 figures.—*Author's abstract.*

173. *Acute Epileptic Dementia.* HAROLD BOURNE, Dunedin, New Zealand. J. Nerv. & Ment. Dis. *122*:288–293, Sept., 1955.

The mental faculties of epileptic persons often steadily decline, and the cause for this decline is uncertain. Three patients are described in whom sudden and lasting dementia followed a calamitous series of convulsions. Two patients had been known previously as epileptics, while the third child was backward, probably having had minor seizures, he had previously taken bromide and had an epileptic father. Reasons are submitted for excluding other diagnoses, for ascribing the brain damage to the convulsive episode preceding it, and for questioning the opinion that convulsions, in themselves, do not injure the brain. Other evidence for such damage is quoted, and a related misfortune with electric convulsive therapy is outlined.

The noxious influence of convulsions is attributed to cerebral anoxia, and the means by which this is brought about are discussed. It is concluded that dementia in epilepsy may be the result of repeated mild injury, probably anoxia, that occurs with convulsions and that the cases here exemplify an occasional similar but massive injury, a syndrome of acute epileptic dementia. It is probably not very rare, and in fact, as illustrated, it is perhaps commonly confused with viral encephalitis as a cause of mental defect. 11 references.—*Author's abstract.*

DEGENERATIVE DISEASES OF THE NERVOUS SYSTEM

174. *Senescence, Senility, and Alzheimer's Disease.* NAOMI RASKIN AND RUTH EHRENBERG Boston, Mass. Am. J. Psychiat. *113*:133–137, Aug., 1956.

The authors report the clinical and neuropathologic findings in 270 patients from 60 to 97 years of age, who represent a cross section of the older patients of a large state hospital. On the basis of the clinical, post-mortem and microscopic findings, the patients were divided into four groups. The first and largest group consisted of 150 patients suffering from arteriosclerotic disease of the brain. The second group of 43 patients from 70 to 95 years of age, had senile atrophy of the brain. The third group of 26 patients, from 60 to 85 years of age, were classified as having Alzheimer's disease because of profound dementia and aphasia and histologic findings of numerous neurofibrillary changes and senile plaques, in spite of advanced age and late onset of illness. (The authors believe that Alzheimer's disease can occur at any age.) The fourth group of 51 patients, from 60 to 92 years of age, were subdivided into those with functional psychosis and those with organic psychosis.

Correlation of clinical and neuropathologic data showed that the largest number of these patients suffered from arteriosclerotic disease of the brain and that psychosis does not always depend on the degree of brain atrophy, that patients with similar brain lesions may present different clinical pictures, and that some patients with pronounced atrophy of the brain may show better compensatory mechanisms than others with less pronounced atrophy. It seems

that three approaches are open now for the prevention and treatment of the psychoses of old age, namely, ultimate control of general arteriosclerosis of which cerebral arteriosclerosis is a part, biochemical studies, and motivation of older people to use their remaining mental resources. 24 references.—*Author's abstract.*

175. *Multiple Sclerosis and the Local Weather.* CARL E. HOPKINS AND ROY L. SWANK, Portland, Ore. A. M. A. Arch. Neurol. & Psychiat. *74*:203–207, August, 1955.

Numerous investigators have noted geographic variations in the incidence of multiple sclerosis, and the causative factors have seemed to be climatic. Others have noted apparent correlation of episodes of exacerbation in multiple sclerosis patients with local weather changes.

A series of 51 multiple sclerosis patients of the chronic-remitting type in Montreal, Canada, were carefully followed for four years, with interviews every one or two months. All evidences of disease activity were recorded. Simple, partial, and multiple correlations were calculated so as to estimate the extent of dependency of the exacerbation rates on various local weather factors, such as mean temperature, diurnal temperature range, day to day changes, humidity, sunshine, solar radiation, wind velocity, and all combinations of these factors.

Findings indicated a low ($r = +0.16$) but significant correlation of diurnal temperature range with multiple sclerosis episodes. The diurnal range represents quick temperature changes within a 24 hour period. The other factors did not correlate with multiple sclerosis activity, but, when they were held constant by partial correlation methods, the correlation of diurnal temperature range rose to $+0.23$, representing a determination by this factor of about 5 per cent of the total variation in multiple sclerosis activity. Thus some 95 per cent of the variation must be attributed to factors other than the macroclimate of the patient's locale. Speculation is offered that a study of the patient's microclimate, i.e., his clothing, housing, and activity, might reveal a somewhat stronger dependence of multiple sclerosis activity on thermal factors. If so, clothing, housing, and activity habits designed to stabilize heat loss in the patient might prove helpful in therapy. 12 references. 4 tables. —*Author's abstract.*

176. *Presenile Cerebellar Ataxia in Chronic Alcoholics.* S. A. SKILLICORN, San Diego, Calif. Neurology *5*:527–534, August, 1955.

A study was made of 6 men with strikingly similar cerebellar dysfunction, characterized by slowly progressive ataxia. They all admitted to prolonged and excessive consumption of alcoholic beverages, and their family histories were uniformly negative. Gross incoordination of the trunk and lower extremities compared to minimal involvement of the upper extremities was particularly impressive, as was the absence of nystagmus. Their ages at the onset of the ataxia ranged from 34 to 55 years (average 47.6). Duration of the illness was one year for 3 men, two years for 1, five years for 1, and 15 years for the other. One patient died in status epilepticus at age 50 after he had been ataxic for one year.

Pneumoencephalograms showed, in addition to distinct atrophy of the cerebellum, marked dilatation of the ventricles and widening of the subarachnoid sulci in each case. Psychologic

evaluation of 5 of the patients revealed definite manifestations of organic brain impairment of a deteriorative type.

Although the report lacks pathologic verification, it concludes that clinically these cases represent diffuse cerebrocerebellar cortical degeneration. It is emphasized that this particular syndrome should be considered in any case of progressive cerebellar dysfunction with onset in the presenium, especially if there is a history of alcoholism, and that the cerebellar syndrome may be but part of a diffuse degenerative process of the entire brain. 45 references. 2 figures.—*Author's abstract.*

DISEASES AND INJURIES OF THE SPINAL CORD AND PERIPHERAL NERVES

177. *Obstinate Hiccup as a Prodromal Symptom in Thoracic Herpes Zoster.* P. EFRATI, Rehovoth, Israel. Neurology *6*:601–602, Aug., 1956.

Only 2 cases have been reported in the literature of the association of hiccups and herpes zoster. A case was presented in which hiccups preceded the appearance of herpes by six days. The skin lesion was localized in the area of the left third to fifth thoracic segments. The usual treatment was of no avail. The hiccups ceased shortly after a single injection of chlorpromazine. It is assumed that the irritation causing hiccups originated in the dorsal ganglion of the afore-mentioned segments. The possible pathways involved were discussed. 9 references.—*Author's abstract.*

178. *Chronic Postherpetic Neuralgia.* LAWRENCE S. VAN BLARICOM AND GILBERT HORRAX, Boston, Mass. J. A. M. A. *161*:511–515, June 9, 1956.

Postherpetic neuralgia is discussed to present experiences in management of this frequent but seldom reported complication. Because of the failure of common medicaments (including narcotics), the neurosurgeon is ultimately called upon to alleviate the severe, intractable pain. This study is based upon 35 patients treated at the Lahey Clinic for 20 years. It was found that postherpetic neuralgia seldom, if ever, appeared before the fourth decade of life. In 68 per cent of these cases symptoms had been present for more than a year.

The herpes virus produces pathologic lesions chiefly in the dorsal root ganglions, but areas of inflammation and degeneration can be observed in the nerve trunks, spinal cord, and skin, producing a central pain syndrome perpetuated finally at the thalamic level.

In postherpetic neuralgia of the trigeminal area 1 of 5 patients benefited from medical management, which consisted of thiamine chloride, nicotinic acid, and tincture of belladonna with phenobarbital. One patient was kept comfortable for seven years by repeated intradermal injections of procaine. Temporary relief of pain was attained in 1 of 2 patients treated with procaine nerve block, and, similarly, 1 of 2 patients improved temporarily when treated with alcohol nerve block. Three of 4 patients obtained temporary relief from peripheral neurectomy. Skin excision gave improvement for an average of two years in 3 patients.

In postherpetic neuralgia involving spinal nerves, medical management, as previously stated, gave 1 of 6 patients temporary improvement; 2 of 8 patients treated by roentgenray

obtained slight relief; 2 of 13 patients obtained long-term relief from intradermal procaine; and others had only temporary relief. Intradermal infusion of sodium chloride improved the condition of 1 patient; intercostal procaine and alcohol blocks did not give prolonged improvement in 9 patients; 3 of 4 patients had marked relief from posterior rhizotomy; and skin excision of painful areas gave marked relief to 1 of 5 patients. Skin undercutting of affected areas gave good relief to 1 of 2 patients; moderate relief was gained by performing a chordotomy in 1 patient and a prefrontal lobotomy in another; and 1 of 3 patients obtained temporary relief from spinal anesthesia. Intrathecally administered alcohol in 1 patient and paravertebral sympathetic block in another gave no beneficial results.

The authors therefore believe that attention should be focused on the preventive aspect of postherpetic neuralgia by reducing the severity of the initial attack with antibiotics and pituitary injection. 11 references. 1 figure. 2 tables.—*Author's abstract.*

ELECTROENCEPHALOGRAPHY

179. *Chlorpromazine and Human Spasticity; an Electromyographic Study.* J. V. BASMAJIAN AND A. SZATMARI, Toronto, Canada. Neurology 5:856–860, December, 1955.

Eighteen patients with spasticity due to upper motor neuron lesions of various types and 5 patients with choreoathetosis were given 50 mg. of chlorpromazine intravenously. Multiple records were made electromyographically before and at intervals after the injection.

There was a rapid and dramatic abolition of spasticity for about two hours in 15 of the 18 spastic patients, but there was no effect in the patients with choreoathetosis. Whatever motor power the patients retained was not affected.

In a detailed discussion of modes of action, it is suggested that chlorpromazine depresses the overbalanced facilitative influences of the brain-stem reticular nuclei, acting downward on the spinal cord as well as upward on the cerebral cortex. Choreoathetosis is not affected unless there is direct depression of the cortex, as with large doses that produce somnolence. 6 references.—*Author's abstract.*

180. *Changing Status of Electroencephalography in Neurologic Practice.* JAMES L. O'LEARY, St. Louis, Mo. Neurology 5:827–846, December, 1955.

An electroencephalography that concerns itself exclusively with seizures and localizing diagnosis cannot fully exploit the manifold uses of the technique. The method should rather be viewed from the broader perspective of an adjunct to the neurologic examination, particularly useful for the contribution it can make in evaluating symptoms pointing to disorder of cerebral origin. Since such symptoms may occasionally reflect systemic imbalances, such as metabolic, endocrine, or electrolyte, if the effect of these on brain activity is not understood, serious errors in interpretation of brain wave tracings may result. For the interpreter who can integrate the findings in the brain wave tracing with history, physical and neurologic examination, and other laboratory data, the procedure makes its most valuable contribution both in diagnosis and in gauging improvement during therapy. Examples are drawn from infancy and childhood, adult life, and the senium.

In infancy and childhood the EEG is of value in deciding which seizure patterns may

arise from a disorder of the brain that is structurally determined in the intrauterine period or after birth. The tracing aids in distinguishing between partial seizures of focal cortical origin and petit mal attacks, and thus may influence the selection of the medication most likely to promote control of the seizures. In stupor, when the antecedent history is vague or indecisive, the EEG may point to an antecedent seizure, or prove a focal disorder of brain activity related to meningitic, encephalitic, or neoplastic causation. With severe headache as the outstanding symptom, the EEG may aid in distinguishing between those cases where neoplasm is the cause and those others in which the headache has a migrainoid or convulsive equivalent basis.

With those whose seizures commence in adult life the EEG can make many valuable contributions. It is important that sporadic seizures on a familial basis may show normal tracings during long seizure-free intervals. Thus a normal tracing does not necessarily rule out a convulsive origin. In certain adults, seizures of recent origin are the first signal for the existence of a brain tumor. It is pointed out that in such instances a tracing obtained too soon after an initial seizure may also be normal. When in doubt, serial tracings are indicated in those instances in which the existence of tumor is suspected. The same rule applies for subdural hematoma. The success of angiography in locating cerebral aneurysms and the many instances in which the EEG alterations are minor, if they exist at all, mean that EEG is not a particularly useful procedure. With headache as the principal symptom, the possibility of a brain tumor should also be entertained. The problem in this instance is to decide on the relatively few instances in which the headache is structurally determined as opposed to the many in which some other causation is likely. It is the headaches of recent origin and severe character that should particularly be screened electroencephalographically. If signs of neurologic deficit are found during the examination, or the history is indicative of associated neurologic symptoms, an EEG examination is always indicated.

Cerebrovascular aging is likely to produce alterations in the electroencephalogram, and instances of disordered tracing are frequently met with in the senium, even in those old people who are neurologically asymptomatic. Vascular occlusions such as occasion hemiplegia or other lateralized neurologic deficit may produce corresponding focal alterations in the electroencephalogram, and these latter may be indistinguishable from those occasioned by a brain tumor or other local process. Following a vascular occlusion, the focal process may gradually disappear, either independently of or accompanying a clearing of the hemiplegia.

Endocrine, metabolic, and electrolyte imbalances and certain neurotoxic manifestations (as bromidism) may occasion both diffuse EEG alterations and cerebral symptoms. Thus, until such possibilities have been eliminated for the particular case, it is unwise to interpret the disordered electroencephalogram as evidence of irreversible cerebral damage. In some instances the cause is readily correctible. 15 references. 15 figures.—*Author's abstract.*

NEUROPATHOLOGY

181. *Cerebral Alterations in Old Age* (*Contribution à la connaissance des différentes altérations cérébrales du grand âge*). F. MOREL AND E. WILDI, Geneva, Switzerland. Schweiz. Arch. f. Neurol. u. Psychiat. *76*:174–223, 1955.

Gross and microscopic studies of the brains of older patients indicate to the authors that

brain involvement follows a precise topographic system peculiar to each lesion. They advance this concept as new and important. Thus the factor of chance loses its importance and will lose more importance as other cases are studied. All of the lesions studied from Alzheimer's disease to massive arteriosclerosis develop according to pre-established laws.

The brain of the older person does not suffer a globular degeneration but rather a systematic atrophy comparable to that seen in Pick's disease, Huntington's chorea, and amyotrophic lateral sclerosis. The atrophy is distinguished from the latter by its appearance in older persons.—*Author's abstract.*

TREATMENT

182. *Methods of Evaluation of New Anticonvulsant Compounds.* J. GORDON MILLICHAP, New York, N. Y. Neurology *6*:484–490, July, 1956.

In view of the diversity of reports on the efficacy of new antiepileptic drugs, the author draws attention to the necessity for controlled studies, and methods of evaluation based on scientific experimental design are described.

A new compound to be accepted for general use must prove more efficacious and less toxic than the established anticonvulsants. Provided that evidence of an anticonvulsant effect has previously been obtained by laboratory and preliminary clinical tests, the action of the trial drug may be compared with that of the currently accepted treatment of choice.

By the use of active medications as controls, the clinical trial is ethical and without hazard, and a significant evaluation of the new drug is made possible. The response to the drug may then be correlated with the etiology, anatomic localization, and clinical and electroencephalographic pattern of the seizures, and a reliable therapeutic classification of seizures may be developed. 12 references.—*Author's abstract.*

183. *Peganone, a New Antiepileptic Drug.* EDWARD D. SCHWADE, Milwaukee, Wis., R. K. RICHARDS, AND G. M. EVERETT, Chicago, Ill. Dis. Nerv. System *17*:155–158, May, 1956.

3-Ethyl-5-phenylhydantoin (Peganone) has been given to 134 patients for 8 to 18 months. These patients were inadequately controlled on previous medication. In 20 the drug was used alone, and in 114 it was added to previous medication. In the series good to complete control of seizures was obtained in 65 per cent. The drug is most effective against grand mal seizures. In combination with other anticonvulsants, it is useful in control of psychomotor attacks. The daily dose is 2 to 3 Gm. for adults and 0.5 to 1 Gm. for children. A notable feature is the low incidence of side effects, less than any anticonvulsant in the authors' experience. No serious toxicity has been seen. No toxic effects on the hematopoietic system have occurred, and liver function tests and urinalysis revealed no deviations from normal values. In 2 patients a mild rash developed, which disappeared in three days on discontinuance of the drug. Since the drug is a hydantoin, the absence of gum hyperplasia and ataxia is of particular interest. Sedation occurred only when high doses were given. It combines well with other antiepileptic drugs, and such combinations often result in control of seizures with no additional side effects. Because of its effectiveness, synergism with other

anticonvulsants, and exceptionally low incidence of side effects, this drug is a valuable addition to the antiepileptic armamentarium. 5 references.—*Author's abstract.*

184. *Use of Meprobamate (Miltown) in Convulsive and Related Disorders.* MEYER A. PERLSTEIN, Chicago, Ill. J. A. M. A. *161*:1040–1044, July 14, 1956.

Meprobamate appears to be of greatest benefit in the control of petit mal seizures, particularly of the idiopathic variety. It may also have some benefit in the treatment of the tense forms of cerebral palsy, some behavior disturbances, and of tension headaches and rheumatoid myositis (fibrositis). It occasionally aggravates grand mal seizures, especially the idiopathic type. It is less effective than trimethadione in controlling petit mal seizures but is at least as effective as paramethadione and 2,2-diethyl-1,3-propanediol and is superior to other drugs that counteract petit mal seizures. Its advantages over trimethadione and paramethadione lie in its relatively innocuous nature; its advantage over 2,2-diethyl-1,3-propanediol lies in the fact that it has a sustained period of reaction and need not be used with retarding agents. 13 references. 2 tables.—*Author's abstract.*

BOOK REVIEWS

Mr. Seward for the Defense. EARL CONRAD. New York, N. Y., Rinehart and Company, 1956. 306 pp. $3.95.

Occasionally a popular book appears, of which this is an example, that is of interest not only to the general public but to psychiatrists as well. Mr. Conrad, who has written several other volumes of contemporary interest, presents here a truly dramatic story, a real life "whodunit," far more satisfying and interesting than most fiction.

In 1846 William H. Seward, an ex-governor of New York, who later became a United States Senator and Lincoln's Secretary of State, defended as a matter of principle William Freeman, an impecunious Negro who had killed several prominent citizens of Auburn, N. Y. This task he undertook in the face of public animosity and even threats of physical harm because he was convinced that the defendent was "insane." The case, although not the first in this country in which insanity had been pleaded as a defense, was probably the most widely publicized to have come upon the scene. Dr. Amariah Brigham, one of the original 13 founders of the American Psychiatric Association and first editor of the American Journal of Psychiatry, testified, and Seward quoted with great effect Isaac Ray's Medical Jurisprudence of Insanity, giving allusions to such writers as Pinel, Esquirol, and Prichard.

Although public excitement brought about the defendent's conviction, the State supreme court reversed the conviction. Freeman died in jail before a new trial could be obtained.

Mr. Conrad tells a vivid story, accurate as to political and racial atmosphere and as to forensic psychiatry, which was then in its infancy. His book is recommended to psychiatrists and to others who enjoy a story with substance.—*Winfred Overholser, M.D.*

Understanding Human Behavior. JAMES L. MCCARTNEY. New York, N. Y., Vantage Press, 1956. 258 pp. $3.50.

This book brings together for the layman what is known about human behavior and what

can be done to help maladjusted persons gain a healthier state of mind. In a commendable attempt to cover a wide field in a compact, highly readable book, a tremendous amount of material is compressed to the point of distortion and the purpose is not achieved.

The digressions into anatomy, endocrinology, electroencephalography, and philosophy are interesting, but they are still digressions. Many statements are controversial (Jews and Chinese have higher and Negroes lower than average intelligence quotients; "injections of male-female hormone combinations give dramatic mental and physical improvement . . . apparently arresting and partially reversing the aging process"), and some are frankly in error. In the chapter on dreams, extrasensory perception and electroencephalography are discussed and connected by such statements as, "Perhaps patients who have delusions and hallucinations are so tense that they do have extrasensory perception and actually do hear or feel things that the normal person cannot."

There are various lists containing all sorts of surprising items. One on instincts lists 47 subtypes; one containing suggestions for hobbies from Americana to zoology includes iron work and gun collecting, but not reading!

The final chapter, entitled "A philosophy for living," after taking issue with religion from St. Paul to Father Divine, turns to some practical advice on getting along in this world and raising children.—*D. A. Starr, M.D.*

The Psychosomatic Genesis of Coronary Artery Disease. DON CARLOS PEETE: Springfield, Ill., Charles C Thomas; Oxford, England, Blackwell Scientific Publications, Ltd.; Toronto, Canada, Ryerson Press, 1955. 220 pp. $7.75.

In this little volume Dr. Peete develops in detail the concept of coronary artery disease as the degenerative end result of chronic recurrent ischemia induced by chronic anxiety, insecurity, and fear. He proposes with conviction that the preventive approach to this ever-increasing problem of our times is a general return to religion and righteousness.

The work reflects a great amount of research into the history of anatomy, physiology, biochemistry, and medicine in general. Illustrations include reproductions of many original plates and drawings from historical works. The format is unusual, each chapter being headed by a quotation from the Bible. He closes by quoting the sentence, "Sufficient unto the day is the evil thereof." The work is at once informative and provocative.—*Otis R. Farley, M.D.*

Group Therapy for Mothers of Disturbed Children. HELEN E. DURKIN. Springfield, Ill. Charles C Thomas, 1954. 125 pp. $3.50.

This small and readable volume is a major contribution to the literature in group psychotherapy. Dr. Durkin, Supervising Psychologist and lecturer for the Post Graduate Center for Psychotherapy, presents what amounts to annotated accounts of her work with mothers who had brought ailing children to the child guidance clinic and found themselves receiving therapy. How she "mobilizes their guilt" and enlists them in active collaboration in analytically oriented group psychotherapy is exciting reading.

Dr. Durkin spells out her concepts, approaches, techniques, and experiences. She thereby renders a great service to group psychotherapists and to psychotherapists in general. An important aspect of this contribution to institutional therapists is the management of the

sick or borderline persons who bring others to clinics for treatment and are currently beyond appropriate medical help. These subjects have their counterparts in relatives of patients in mental hospitals, prisoners, and the steadily larger segment of the population acknowledged to be in need of preventive psychiatry.—*Joseph Abrahams, M.D.*

Neurology and Psychiatry in Childhood. Edited by RUSTIN MC INTOSH AND CLARENCE C. HARE. Research Publication No. 34, Association for Research in Nervous and Mental Disease. Baltimore, Md., Williams & Wilkins Co., 1954. 504 pp. 63 illus. 21 tables. $11.00.

This volume constitutes the report of the Proceedings of the Association, held in 1954. The contents are comprehensive: Infections of the Central Nervous System, Developmental and Traumatic Aspects, Functional and Degenerative Disturbances, Roentgenographic Aspects, Psychiatric Aspects, and a Symposium on Juvenile Schizophrenia. Each part (two to six papers) is followed by a discussion. The authors represented, and the discussants, too, are prominent in the field. Thus, we have an authoritative presentation of the numerous aspects of the topic. The volume is printed on highly calendered paper and is in every way up to the high standards of the Association and their publishers.

—*Winfred Overholser, M.D.*

Police Drugs. JEAN ROLIN. Translated by L. J. Bendit. New York, N. Y., Philosophical Library, Inc., 1956. 194 pp. $4.75.

This is an extensive study by a French author of the use of drugs as a means of extorting confessions. It takes as its point of departure a case (that of Henri Cens, an alleged collaborator) and the use in that case of thiopental sodium as a means of "unmasking" a malingerer. The author violently attacks the use of the drug and the inferences drawn from the results of its administration—an attitude entirely consistent with the American point of view. Confession after use of thiopental is "a surrender to force or to trickery, a surrender even of the freedom whether to surrender or not; so it is a double degradation" (p. 121).

The book is a searching one and adduces the various and cogent reasons for not using drugs for police purposes. There is an extensive bibliography to which the reviewer would add Despres' "Legal Aspects of Drug-Induced Statements" (14 U. of Chicago L.R. 601 [1946]) and the study by Dession, Freedman, Donnelly, and Redlich entitled "Drug Induced Revelation and Criminal Investigation" (62 Yale L.J. 315 [Feb., 1953]).

The reading of the volume is recommended for all who are interested in the work of police and prosecutors.—*Winfred Overholser, M.D.*

Crime, Courts and Probation. CHARLES L. CHUTE AND MARJORIE BELL. New York, N. Y., 1956. The Macmillan Co. 268 + xiii pp. $4.75.

Probation is so widely accepted today as an important part of the correctional process that it is hard to realize it is relatively an innovation. Beginning in 1841 in Boston with the dedicated work of John Augustus, it has spread, received statutory recognition, and become a well-developed system. It is through the development of probation that psychiatry has

been introduced into the treatment process in the field of juvenile delinquency and criminal law. For that reason, and for its general social importance, this book is of interest to psychiatrists.

The late Charles L. Chute not only witnessed the growth of the concept of probation in its crucial years but also was an important actor in the drama, enlisting the interest of representative citizens and extending the acceptance of probation. He was Executive Director of the National Probation Association from 1921 until 1948. Mrs. Bell, the co-author, was closely associated with the work of the Association for many years as well. Thus we have an authoritative account of the development and growth of a highly valuable step forward in correctional treatment. The book carries an introduction by Roscoe Pound, Dean Emeritus of the Harvard Law School, an outstanding teacher and philosopher of law.

Mr. Chute and Mrs. Bell have written a volume of value to students of the social scene.

—*Winfred Overholser, M.D.*

Taboo. FRANZ STEINER. New York, N. Y., Philosophical Library, Inc., 1956. 154 pp. $4.75.

This is a brief, carefully reasoned, and rather subtle book of particular value to the nonspecialist. The thesis developed by Dr. Steiner is that the idea of taboo in Western thought has been heavily conditioned by Victorian and contemporary values. He deals critically with a number of different views including those of Freud, although the bulk of the work is concerned with that of Robertson-Smith and Fraser. He rejects Freud's argument that a meaningful analogy may be drawn between taboos and obsessive-compulsive symptomatology, an analogy which is of critical importance in "Totem and Taboo."

The author's own contribution is a brief statement to the effect that taboos would appear to have the function of localizing danger. By forming situations fraught with danger, they enable the group to deal with them effectively. Unfortunately his own remarks are made tangentially and are not elaborated upon and we are permitted only a glimpse of what would appear to have been an extraordinarily lucid and sharp intelligence.

—*Thomas D. Reynolds, M.D.*

The Relationship Between Syringomyelia and Neoplasm. CHARLES M. POSER. Springfield, Ill., Charles C Thomas, 1956. 98 pp. $3.50.

A comprehensive analysis of 234 autopsy cases is presented in which syringomyelia was found associated with neoplasm of the central nervous system. Of these cases, 224 were from the literature and 10 were found in the files of the New York Neurological Institute.

The age, sex, and location of the cavity was tabulated. The lumbosacral segments were found to be involved in one eighth of the patients, and the entire cord in almost one-fourth. The concurrence of central nervous system neoplasm and syringomyelia is not a chance phenomenon. The author concludes that the association of these two lesions can best be explained on the basis of congenital anomalies resulting from faulty closure of the dorsal raphe with glial or mesodermal inclusions at the site of the faulty closure or at other locations in the central nervous system. It is suggested that a similar process may result in phacomatosis of one kind or another.—*Harold Stevens, M.D.*